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An international publication for the study of the circulation

George E Burch *Editor*

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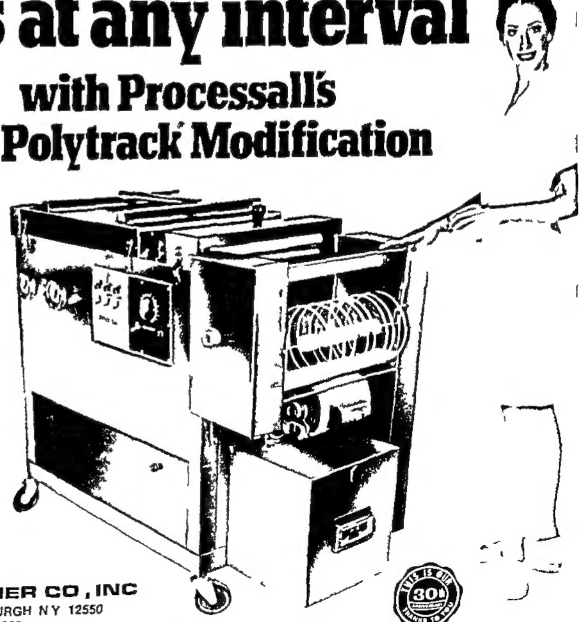

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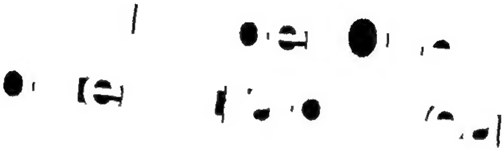

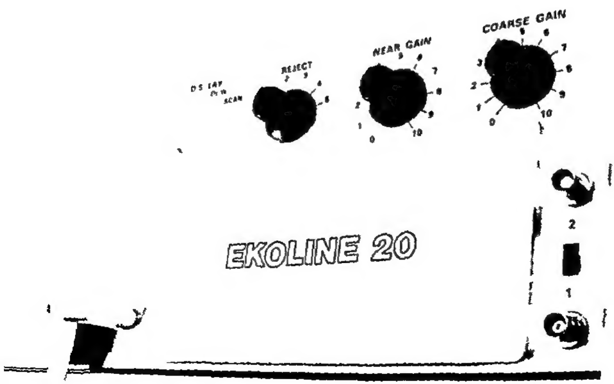
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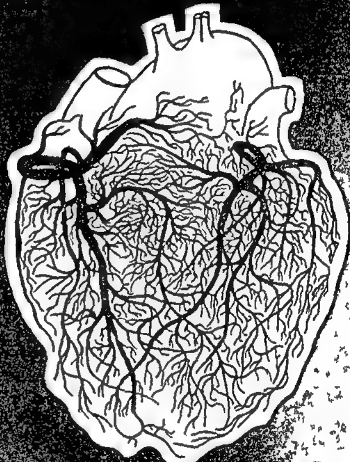

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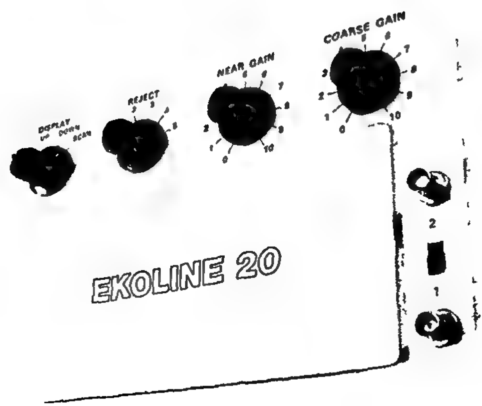
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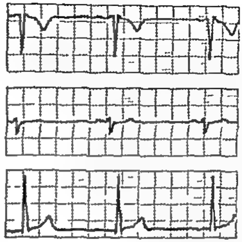

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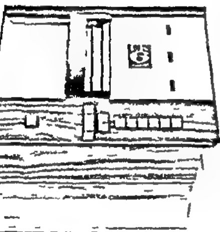

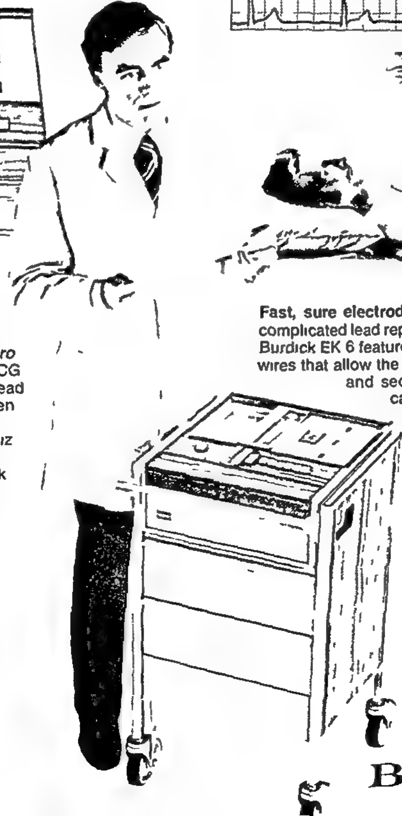

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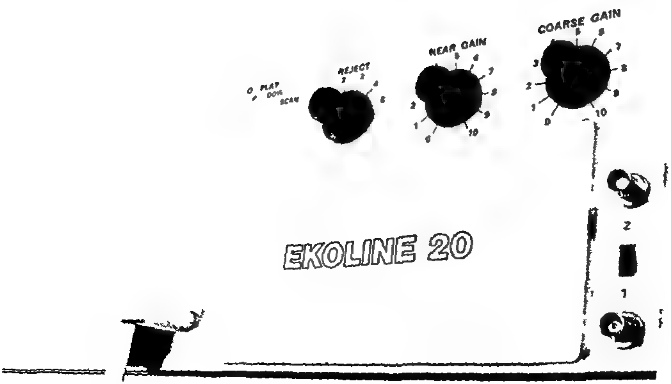
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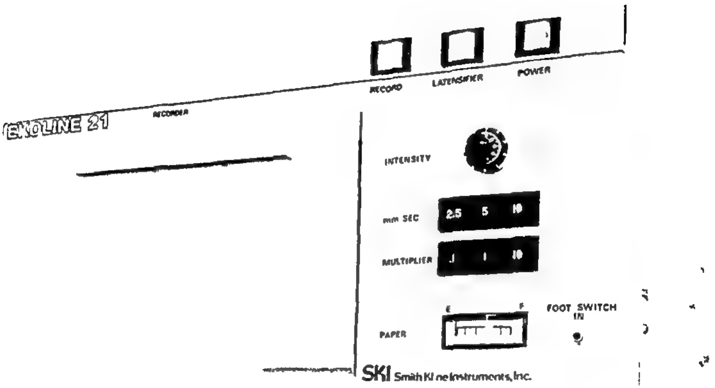

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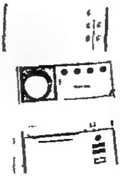

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Editorial

Sudden death and acute myocardial infarction — What are we talking about?

William J Grace M D *
New York N Y

Sudden death outside the hospital is very common in our country Vital statistics indicate that there are as many as one half million people who die this way every year However vital statistics record that the bulk of such deaths are due to an acute myocardial infarction [1] In spite of this rather well entrenched tradition there is some question about whether this is the truth For example the study of sudden death done in Baltimore by Kuller and associates[2] reports that 61 per cent of the patients have at autopsy only arteriosclerotic heart disease 14 per cent have alcoholism and fatty liver and the rest of the deaths are due to a variety of causes Fifty per cent of the patients who have sudden deaths have extensive severe coronary artery disease In this particular study of sudden death only 13 per cent of patients had an acute myocardial infarction Therefore to say that sudden death is due to acute myocardial infarction is far from being accurate

Roberts and Buja have recently reviewed the problem They made a meticulous dissection of coronary arteries in patients who died within a few hours of the onset of symptoms Coronary thrombosis or acute myocardial was not present in any significant number of the patients

In this regard there is a special experience reported by Cobb and colleagues (Seattle Washington) who treated a number of patients in ventricular fibrillation outside of the hospital These patients were promptly defibrillated and 20 per cent survived to leave the hospital in good condition In this particular report very few of these patients had electrocardiographic evidence of acute myocardial infarction Liberthson and co workers[3] (Miami Florida) report similar findings in patients outside the hospital

It is therefore important to realize that the patient who died suddenly outside of the medical care system did not die of an overwhelming and irreversible myocardial necrosis but that he died in all probability from cardiac arrhythmia The type of arrhythmias seen is the type seen in Coronary Care Units and is predominantly that of ventricular fibrillation ventricular tachycardia and occasional bradyarrhythmias with hypotension Inasmuch as these arrhythmias are treatable we must give considerable thought to instituting systems in our community for arrhythmia control and cardiopulmonary resuscitation

A study by Geddes and associates[4] indicates that those patients with acute myocardial infarction and ventricular fibrillation had as smooth a post hospital course as those who did not have ventricular fibrillation A one year follow up indi

From the New York University School of Medicine and St. Vincent Hospital and Medical Center New York, N Y

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Reprint requests to Dr William J Grace St. Vincent's Hospital and Medical Center of New York, 153 W 11th St New York N Y 10011

*Director Department of Medicine St. Vincent Hospital and Medical Center of New York Professor of Clinical Medicine New York University School of Medicine

cated that there was no disadvantage to the patient who had been resuscitated from ventricular fibrillation with success

Of particular note is experience in ambulancing throughout the world. Reports which have been summarized by Lambrew[7] indicate that in such places as Baltimore, Belfast, Charlottesville, Maryland, North London, and Rochester, a per cent of patients have cardiac arrest in the ambulance; this per cent is not insignificant and varies from 8.7 per cent reported from Montgomery County, Maryland, to as high as 17 per cent (Virginia) and 21.7 per cent (North of London). It is presumed that these deaths are likewise arrhythmic deaths. This is an additionally sad event, for here the patient is under some kind of a medical care system which is seemingly unable or unauthorized to deal with ventricular fibrillation.

Lambrew[7] has transmitted ECG's on all patients transported to the hospital by the rescue squad in Suffolk County, New York. A surprisingly large number of life threatening arrhythmias occur in the patients who seemingly have called the ambulance solely because of trauma or automobile accident. In the chest pain patients, cardiac arrhythmia was recorded in 22 per cent. Eight per cent had ventricular fibrillation as the initial rhythm, e.g., in 2,744 patients for whom the ambulance responded because of a call of trauma, 4.2 per cent had a significant cardiac arrhythmia recorded. The initial arrhythmia was ventricular fibrillation 0.1 per cent and 0.2 per cent ventricular standstill. Cardiac arrest occurred in transit in this ambulance study—in patients with chest pain (1 per cent of 1,728 patients) and in trauma patients (.03 per cent of 2,744 patients). Although the number of arrhythmic deaths in trauma patients is statistically small, nevertheless it is an extremely important observation. Arrhythmia control and cardiopulmonary resuscitation are necessary for the ambulance teams even when approaching a patient whose only problem presumably is trauma. Hence it behooves all practicing physicians to be aware of the fact that sudden death is associated with lethal cardiac arrhythmias, and that importantly this may occur in the setting of trauma, as well as in the setting of symptomatic coronary artery disease.

Physicians should be concerned about out of hospital deaths and should be actively engaged in a community organization to solve this therapeutic problem.

Reports from Drs. Pantridge and Geddes[6] in Ireland, Drs. Grace and Chadbourn[9] in New York City, Dr. Cobb and associates[4] and Drs. Rose and Press[10] in the far West and Dr. Lewis and colleagues[11] in Ohio all indicate that out of hospital rescue squads are effective in salvaging patients from ventricular fibrillation. Reports from our own experience[9] indicate that beginning coronary care outside the hospital lowers the hospital mortality rate.

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Clinical communications

Reciprocal rhythm in patients with normal electrocardiogram Evidence for dual conduction pathways

Paul Touboul M D
Félix Huerta M D
Jacques Porte M D
Jean Pierre Delahaye M D
Lyon France

The use of electrical stimulation of the heart in man has made it possible to identify a group of tachycardias which can be initiated by prematurely induced atrial or ventricular beats and stopped in the same way [1,2] This type of response has been explained on the assumption of a circular movement of excitation in the atrioventricular (A V) junction In the Wolff Parkinson White (W P W) syndrome reciprocating tachycardias are likely to occur as a result of circus movement between two anatomically distinct pathways normal A V conducting fibers and Kent bundle [3,4] Another possibility calls for re entry within the A V node itself [5] Studies by Mendez and Moe [6] Watanabe and Dreifus [7] and Janse and co workers [8] have provided experimental support for the hypothesis of circular intranodal movement The mechanism of A V nodal re-entrance is still debated Impulse reflection resulting from depressed conduction [9] or dual A V pathways are usually invoked In patients with paroxsymal supraventricular tachycardia electrophysiological studies may help to identify the actual mechanism of re-entrant activity In this regard a recent report by Denes and co workers has stressed the role of dual A V nodal pathways in the genesis of reciprocal rhythm The present work reinforces this idea by providing further electrophysiological data It was performed between November 1973 and April 1974 in the Hôpital Cardiovasculaire of Lyon

From the Laboratoire d'Electrophysiologie Hôpital Cardiovasculaire et Pneumologique Lyon, France

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Reprint requests to Paul Touboul M D *Hôpital Cardiovasculaire et Pneumologique* H P Lyon Montchat, 69394 Lyon Cedex 3, France

Materials and methods

Six patients were studied four men and two women whose ages ranged from 24 to 63 years (average 47) A reciprocal A V rhythm could be proved in each case in four cases it was responsible for sustained tachycardias QRS was always normal and the P R interval at least equal to or more than 0 13 second

The electrophysiological studies were performed in the postabsorptive nonsedated state Under local anesthesia four electrode catheters were introduced percutaneously via the right and left femoral veins The electrical activity of the His bundle was recorded according to the method of Scherlag and co workers [12] Of the two electrode catheters positioned in the right atrium one was used for recording a bipolar electrogram at junction of the superior vena cava and the right atrium the other was used for stimulating electrically the right atrium at the upper third of the septum The right ventricle could be paced by means of a bipolar electrode catheter positioned at the apex. The records were obtained with an 8 channel direct ink writing jet recorder* at a paper speed of 100 to 200 mm per second The distal terminals of the tripolar electrode catheter were led into the A C input of an electrocardiogram (ECG) amplifier His bundle activity was recorded at a frequency setting of 40 to 700 c.p.s A programmable modular stimulator† was used Rectangular pulses of 1.5 msec duration were delivered at twice diastolic threshold intensity

The study included atrial pacing at increasing

*Elema-Schönander
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Table I Conduction times in Patients 1 to 6

Case No	Conduction intervals (msec)			
	P R	P A	A H	H V
1	145	20	75	50
2	175	50	75	50
3	160	30	80	50
4	130	15	80	35
5	135	20	70	45
6	140	25	55	60

Table II Evolution of AH conduction time during atrial pacing

Cycle length (msec)	AH conduction time (msec)					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
850		70				
750	85	70	90			
650	100	125				
600	115	300*	95			60
575	120					
550	300		105			60
525						
500			115	80		65
450				80	115	75
425			120	80	120	80
400			180	80	130	160†
375				80	200‡	
350				80		

*Unstable AH which then shortens Final lengthening at a 525 msec cycle
†Unstable AH then permanently long
‡Unstable AH long then short lengthening finally at a cycle of 2 5 msec

Table III Refractory periods of the fast pathway and of the slow pathway

Case No	Cycle length (msec)	Refractory period (msec)		
		Fast pathway		Slow pathway
		FRP	FRP	ERP
1	750	520	450	370
2	900	565	490	340
3	750	390	340	< 270
4	500	330	305	< 250
5	500	395	345	< 190
6	600	380	340	< 250*

*Here the limiting factor of A V conduction is the effective refractory period of the atrium The numerical values correspond to the shortest A1A2 intervals obtained FRP Functional refractory period ERP effective refractory period

rate, and extrastimulus method with premature atrial response induced at every eighth beat The same sequence was then performed at the ventricular level

Definitions

H stands for the His bundle deflection, A and V for atrial and ventricular electrograms

During extrastimulus procedure A1 H1, and V1 concerned the basic beat, A2 H2 and V2 the premature response The shortest possible H1H2 interval defined the functional refractory period of the A V node The longest A1A2 interval so that A2 was not propagated to the His bundle measured the effective refractory period of the A-V node Finally the longest S1S2 interval so that S2 was not followed by atrial response corresponded to the effective refractory period of the atrium

Results

The information concerning the basic conduction times in the six patients is contained in Table I The responses provided by the extrastimulus method have common features which can be summarized as follows At first, while the coupling interval was gradually reduced, the delay sustained by the premature beat in the A V junction remained slight If the H1H2 responses were plotted against the A1A2 intervals the points obtained at this stage deviated little from the line of no A V nodal delay (Fig 1) At a critical A1A2 interval corresponding on average to 60 per cent of the basic cycle length, the A2H2 conduction time of the six patients suddenly lengthened by 110 115 70 70 30 and 55 msec respectively (Figs 2 and 3) The H1H2 response curve then showed a break and shifted upward isolating a second group of points This part of the curve included the initiation zone of atrial echoes (cases 1 3 4, and 6) and of reciprocating tachycardias (cases 2 and 5) It should be noted that in one case (case 3) the increasing of A2H2 allowed the His Purkinje conduction to resume

Atrial pacing at increasing rate in one case (case 4) gave rise to a 1 1 A V conduction with fixed P R interval up to 170 per minute In all the other cases, after an initial phase in which the A V delay varied very little at a critical rate an abrupt increase in the A H time occurred reaching nearly 200 msec in Patients 1 and 2 (Table II) This change was sometimes accom

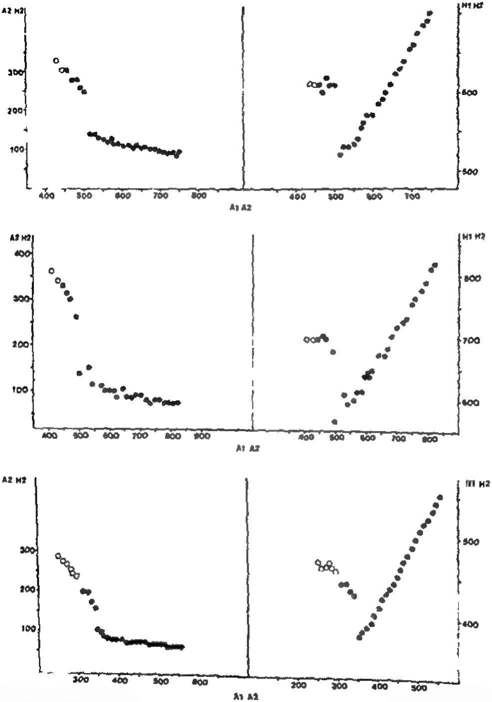

Fig 1 Three representative curves of the H1H2 and A2H2 responses plotted against the A1A2 intervals Top case 1 middle case [redacted] bottom case 3 The times are in milliseconds The open circles correspond to the echo zone For further details see text

panied by a period of instability with intermittent return to short A V conduction times (cases [redacted] and 6 Figs. 4 and 5) It usually preceded the occurrence of reciprocal rhythm

Ventricular pacing was always followed by retrograde conduction to the atria V A conduction time did not change as a result of accelerated rate only Patient [redacted] showed an increase of 15 msec between 90 and 150 per minute In two cases at 160 per minute a second degree V A block appeared Mobitz type 2 (case 3) and 2 1 (case 2) In Patient 5 paired ventricular stimula

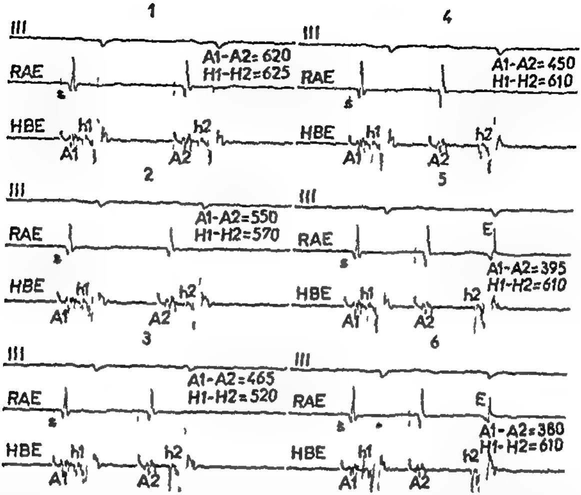

Fig 2 Case 1 Extrastimulus method Up to a coupling interval of 465 msec the A V nodal delay of the premature beat remains slight At 450 msec an abrupt lengthening of the A2H2 interval occurs followed by the occurrence of atrial echoes *S* Stimulus *RAE* right atrial electrogram *HBE* His bundle electrogram

tion induced an attack of reciprocating tachy cardia (S1S2 interval = 320 msec) It is note worthy that the premature beat was not accom panied by a prolongation of the retrograde delay (Fig 6) In the other cases this procedure had no effect

Discussion

The results of this study suggest the existence of a dual A V conduction system, composed on the one hand of a fast pathway with a long effective refractory period and on the other of a slow pathway with a short effective refractory period The response to atrial extrastimuli can be interpreted according to this outline When the A1A2 interval was sufficiently long, the A V conduction time was linked to the transmission of the impulse by the fast pathway Then a break in the curve of the H1H2 responses occurred in relation to the sudden slowing of the premature beat proximal to the His bundle activity It is tempting to consider that the A1A2 interval at which this change occurred measured the effec tive refractory period of the fast pathway, the shortest H1H2 interval being the functional refractory period Afterward the impulse fol lowed only the slow pathway, favoring the initia tion of a circus movement between the two pathways The echo zone was included in the second part of the H1H2 interval curve corre sponding to the slow responses The refractory periods of the two pathways measured in the present series are to be found in Table III

The influence of the basic cycle length on the response to the extrastimulus has been stressed by Denes and co workers,[11] who noticed in a patient that the break in the H1H2 or A2H2 curves occurring at an induced cycle of 667 msec was no longer found in sinus rhythm (cycle length 750 msec) They interpreted this fact by suggesting that the effective refractory period of the fast pathway, shorter than that of the slow

pathway at low rate overtook the latter when the rate became faster In two patients of this series (1 and 3) the extrastimulus method was per formed at two induced basic cycles successively 750 and 600 msec In case 1 the appearance of the curves remained unchanged the refractory peri ods of both pathways increased as the cycle became shorter In case 3 at 600 msec no break was apparent the refractory period of the fast pathway becoming the shortest echo beats could not be induced in these conditions

During atrial pacing the passage without transition from short to long A H interval rein forced the hypothesis of two pathways having different conduction velocities The functional exclusion of the fast pathway which coincided with the lengthening of AH was followed by atrial echoes or reciprocating tachycardia

The response to ventricular pacing points in the same direction Retrograde conduction to the atria was constant The fixed V A time whatever the rate suggested a bypass of the A V node The induction of tachycardia by a premature ventric ular beat without lengthening of the V A conduc tion time (Patient 6) was hardly consistent with a reflection of the impulse in an A V nodal area during the relative refractory period A more plausible explanation assumes a circus movement between two pathways initiated by retrograde block in one of them In this regard it should be stressed that Coumel and co workers[3] while studying 26 patients suffering from paroxysmal supraventricular tachycardia in the absence of W P W syndrome were able to induce tachy cardia by one or more ventricular premature beats in 15 of the patients If in 12 cases V A conduction time lengthened before the onset of the arrhythmia in three cases it remained unchanged

Accessory fibers connecting the atria directly with the lower part of the A V node or with the His bundle have been described anatomically[1] They are the basis of the Lown Ganong Levine syndrome as a recent pathological study has confirmed The short PR interval is then the proof of accelerated atrio His bundle conduction The occurrence in these circumstances of recipro cating tachycardia implies a circular movement of the impulse between the normal and accessory pathways. In the cases reported the attacks occurred after a premature atrial beat with a

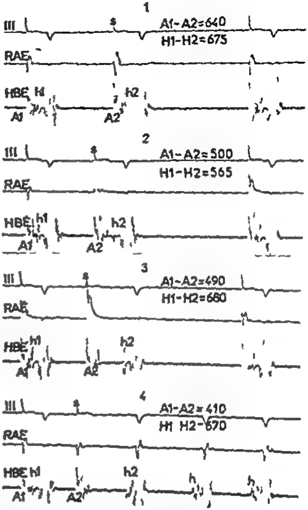

Fig 3 Case 2 Extrastimulus method When the A1A2 interval is reduced from 500 to 490 msec the A2H2 conduc tion time increases by 115 msec Further increase of the A V nodal delay is followed by tachycardia

prolonged PR interval[8,11] It must be assumed that in the antegrade direction the impulse was transmitted along the A V node and the His bundle and returned to the atria via the anoma lous connections Recently Coumel and co work ers[7] enlarged the definition of this syndrome by including in it all the cases in which whatever the length of PR the possibility of dual pathways was strongly suggested by the methods of stimu lation These authors gave the following as char acteristic features (1) shortness of the PH inter val (2) remarkable permeability of the A V conduction system with 1 1 transmission up to high rates (3) abrupt changes in A V and V A conduction time during cardiac pacing (4) occa

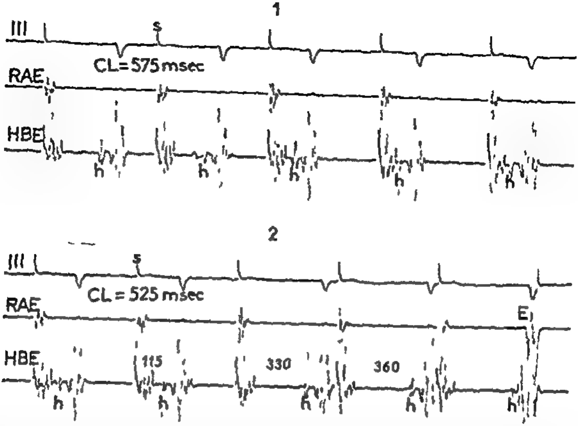

Fig 4 Case 2 Atrial pacing At an induced cycle of 575 msec alternating long and short AH intervals may be observed in the upper tracing At 525 msec *(lower tracing)* the AH interval suddenly lengthens. *The increase of the* A V nodal conduction time gives rise to an atrial echo *CL* cycle length *115 130* and *150* AH conduction time (in milliseconds)

sional blocking of premature atrial beats distal to His bundle activity A V conduction may resume at shorter coupling intervals however, this is the gap phenomenon during which the increase of the A V nodal delay allows the subjacent tissue to recover at the arrival of the impulse[18] These authors found a reciprocal rhythm in only one case out of 15 while atrial flutter and fibrillation were usual Thus certain data collected in the present series are consistent with the idea of A V nodal by pass

Analyzing the initiation of reciprocal rhythm by the *extrastimulus method Goldreyer and* Damato[19] *recorded responses marked by a* progressive increase of the A V nodal conduction time As soon as the A2H2 interval was long enough tachycardia occurred At first sight these cases suggested a reflection mechanism within the A V node In fact it is possible once again to imagine two pathways with unidirectional block of the fast pathway From a given A V nodal delay, the impulse which enters the fast pathway in a retrograde direction may re excite the atria outside the refractory period The hypothesis agrees with recent observations of reciprocating tachycardia in which a circus movement involving a Kent bundle was assumed despite the absence of W P W syndrome during sinus rhythm[20, 21] Thus further progress in electrophysiology might result in a reappraisal of the concept of A V nodal re entrance in man

Summary

The present study refers to six *patients in* whom an A V reciprocal rhythm *could be docu*mented, *in four cases it took the form of sustained tachycardia None of the patients* showed any ECG feature *of ventricular pre excitation* (PR interval of more than 0 12 sec and normal QRS configuration) The extrastimulus method showed at first that the A V conduction time of the premature beat varied only slightly with the decrease of the coupling interval From a critical A1A2 interval there was a sudden lengthening of A2H2 preceding the occurrence of re entrant beats The curve of H1H2 responses *reflected* these changes showing two *distinct parts* The second part *following the slowing of the impulse included the initiation zone of atrial* echoes and of *reciprocating tachycardia* These results suggest

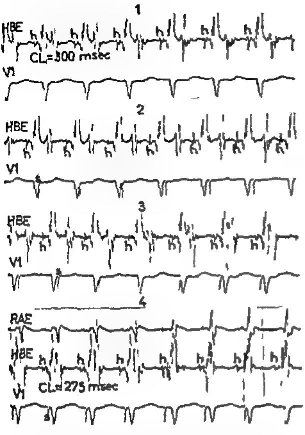

Fig 5 Case 5 Atrial pacing At an induced cycle of 300 msec the AH interval which was long at first shortens and then lengthens again (strips *1 2* and *3*) Bottom at a higher pacing rate the cessation of stimulation reveals tachycardia

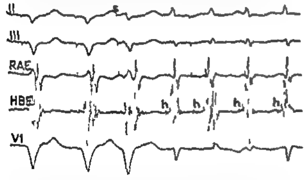

Fig 6 Case 5 Paired ventricular stimulation The premature beat induces tachycardia in spite of the absence of any lengthening of the V A conduction time The second and third beats of tachycardia show different degrees of ventricular aberrancy

the existence of two A V pathways one fast and the other slow The point at which the break between the two parts of the curve occurred might be related to the effective refractory period of the fast pathway In the same way when atrial pacing reached a critical rate it induced an abrupt increase of AH in five cases In the sixth patient A V conduction time remained unchanged up to 170 per minute Ventriculoatrial conduction was always observed the delay of which did not lengthen with the rate In one case tachycardia could be induced by a premature ventricular beat without lengthening of the V A time It is concluded that in spite of a normal PR interval the presence of dual A V pathways may be implied in the genesis of reciprocal rhythm

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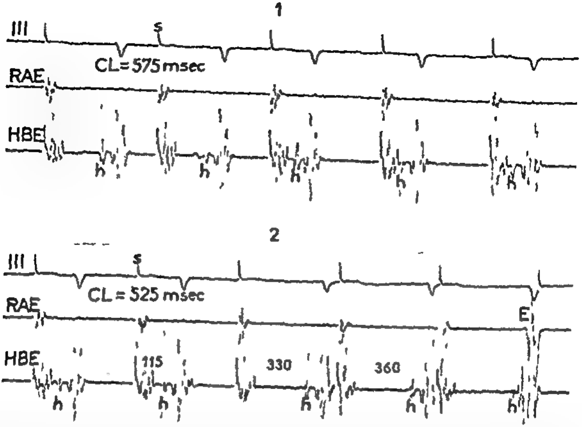

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Electrocardiographic and hemodynamic correlations in patients with idiopathic hypertrophic subaortic stenosis

Abe Walston II M D
Victor [illegible] Behar M D *
Galen [illegible] Wagner M D
Joseph C Greenfield Jr M D **
Durham N C

Patients with idiopathic hypertrophic subaortic stenosis frequently have electrocardiograms (ECG) and vectorcardiograms (VCG) which meet diagnostic criteria for left ventricular hypertrophy ventricular conduction delay and/or myocardial infarction The ECG changes which simulate myocardial infarction have been ascribed to asymmetrical septal hypertrophy abnormal myocardial cell architecture and/or degeneration of the abnormal septal muscle cells which have been shown in patients with idiopathic hypertrophic subaortic stenosis [3] However only a few patients have been reported in whom the absence of coronary disease has been documented by either cardiac catheterization or postmortem examination [9] In addition despite numerous descriptive reports of ECG findings associated with idiopathic hypertrophic subaortic stenosis the correlation of hemodynamic findings with the ECG has been rarely presented [10]

This report describes 33 patients with documented idiopathic hypertrophic subaortic stenosis and normal coronary arteries in whom a correlation between the ECG and VCG findings and the hemodynamic and anatomic characteristics have been demonstrated

F om the Veterans Admini t t o Hospital and the Department f Medic n (D vis n of Card ology) Duke Uni rs ty Med cal Cente Durh m N C

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Methods

Forty four patients with idiopathic hypertrophic subaortic stenosis (IHSS) were studied hemodynamically at Duke University Medical Center between July, 1969 and December 1973 In 31 of these patients coronary artery disease was excluded by selective right and left coronary arteriograms In addition two patients 26 years of age were included in this data analysis because of the small likelihood of the presence of coronary disease thus the study population consisted of 33 patients The ages ranged from 23 to 64 years and the male/female ratio was [illegible] 1 Congenital and valvular heart disease was excluded in all patients by right and left heart catheterization and left ventricular cineangiography One patient (M D) with a small secundum atrial septal defect and negligible left to right shunt was included Whenever possible left ventricular inflow tract pressure was measured (transseptal left atrial puncture) to insure accurate measurement of a true intraventricular gradient and to exclude catheter entrapment To avoid any misdiagnosis caused by possible catheter entrapment the diagnosis of IHSS was established only when in addition to an intraventricular gradient (rest or provocation) one of the following was documented (1) post premature ventricular contraction (PVC) diminution in the arterial pulse pressure at rest or following provocation (amyl nitrite or isoproterenol) (26 patients) or (2) the angiographic demonstration of movement of the anterior leaflet of the

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Table I Hemodynamic and angiographic data in Group I patients

Pt.	*ECG VCG*	*Rest gradient (mm. Hg)*	*Maximum gradient (mm. Hg)*	*Post PVC*	*Ant. MVM*	*Mitral insuf*	*Ventricular wall*	*Papillary muscle*
D. T.	NL	0	87	Pos.	No	0	Normal	Normal
A. B.	NL	0	34	Pos.	No	0	Normal	Normal
W. S.	NL	0	113	Neg.	Yes	0	Normal	Mild
M. Mc	NL	0	58	Pos.	No	0	Mild	Normal
M. J.	NL	0	110	Pos.	No	0	Normal	Normal
B. P.	NL	0	114	Pos.	Yes	0	Normal	Normal
M. D.	NL	0	155	Pos.	Yes	0	Normal	Normal
W. S.	NL	0	100	Pos.	Yes	0	Normal	Mild
R. T.	IMI	0	100	Pos.	Yes	0	Normal	Normal
N. K.	IMI	0	25	Pos.	No	0	Normal	Normal
G. F.	IMI	0	72	Neg.	Yes	0	Moderate	Severe

Column 2 shows the ECG and/or VCG classification either normal (NL) or inferior myocardial infarction (IMI). Rest gradient (column 3) refers to left intraventricular gradient at rest and maximum gradient (column 4) refers to the maximum gradient obtained either at rest or with amyl nitrite or isoproterenol stimulation. In column 4 asterisk (*) signifies isoproterenol and dagger (†) signifies amyl nitrite stimulation. In column 5 a decrease in the arterial pulse pressure amplitude in the beat following a PVC is called a positive response. A positive response followed by an asterisk (*) denotes that the response occurred only after amyl nitrite or isoproterenol stimulation. In column 6 the patients with movement of the anterior mitral valve leaflet into the outflow tract during ventricular systole are termed yes, and those without are termed no. Mitral insufficiency (column 7) was graded 0 to 4+ by standard cineangiographic techniques. Hypertrophy of the ventricular free wall and papillary muscles (columns 8 and 9) were graded by cineangiographic analysis.

patients in the supine position using a Hewlett Packard automatic cardiograph (1515B). VCG's were recorded on 26 patients with the Frank lead system using a Hewlett Packard 1507A vectorcardiograph. Chest electrodes were placed at the fourth intercostal space as recommended for the supine position.[3] Photographs of the frontal, transverse, and left sagittal planes were taken directly from the oscilloscope using Polaroid type 107 film. The VCG traces were interrupted at 2.5 msec. intervals and a calibration of 1 mv./2 cm. deflection was used. The initial portion of the QRS loop was enlarged on separate photographs with P and T loops excluded, using a calibration of 1 mv./10 cm. deflection to facilitate analysis of the initial forces. All of the ECG's and VCG's were taken within 2 weeks of cardiac catheterization.

ECG's were classified as left ventricular hypertrophy (LVH) using the point score system of Romhilt and Estes and VCG's were classified as LVH when the maximum transverse plane amplitude was ≥ 2.2 mv. below age 50 or ≥ 1.8 mv. above age 50 and transverse T loop angle ≥ 70 (modification of the criteria of Romhilt and associates). The ECG diagnosis of anterior myocardial infarction (AMI) was established using standard criteria and the VCG diagnosis of AMI was made if the 15 msec. point was posterior in the transverse plane. The VCG diagnosis of inferior myocardial infarction (IMI) was established by superior deviation of the initial forces meeting the criteria of Starr and associates.[7] No patient was included with right or left bundle branch block.

Hemodynamic data of the two patient groups were compared using Student's t test for unpaired data on an IBM 1130 computer.

Results

The patients were divided into two groups according to the absence (Group I) or presence (Group II) of left ventricular hypertrophy (LVH) on the ECG and/or VCG. Group I was composed of the 11 patients who did not have ECG evidence for LVH. Classification utilized the ECG alone in three patients and both the ECG and VCG in eight patients. The ECG and VCG were normal in eight patients and met criteria for inferior infarction in three. The three patients without a VCG had a normal ECG and in no patient was there disagreement between the ECG and VCG findings.

Group II was composed of the 22 patients who exhibited left ventricular hypertrophy on their ECG and/or VCG. Classification was done using both ECG and VCG in 18 patients and using the ECG alone in four patients. In addition to LVH, one patient met criteria for anterior infarction, one for inferior infarction, and three for both anterior and inferior infarction. The mean trans-

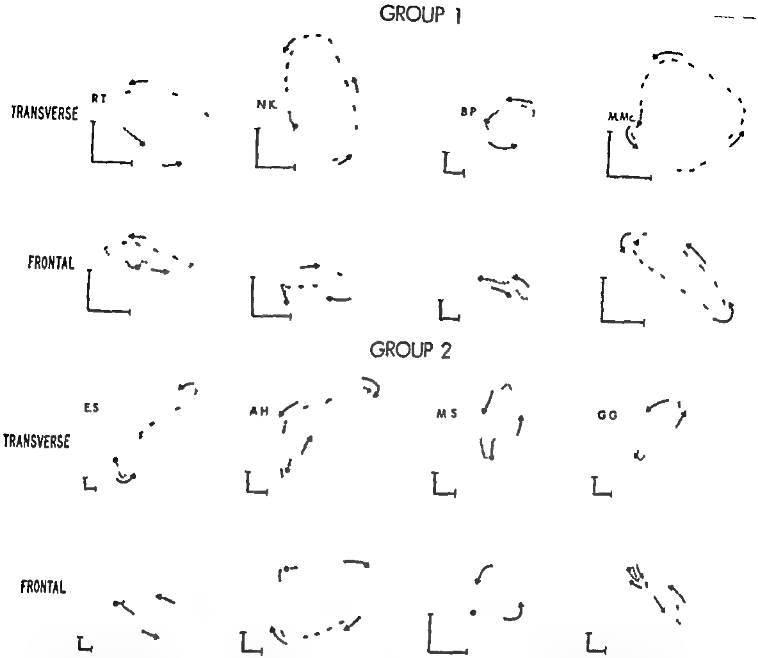

Fig 1 Frontal and transversal plane projections of the Frank ECG are shown for four representative patients in each of Group I (upper) and Group II (lower) Calibration bars (0 5 mv) are shown for each axis VCG traces were interrupted at 2 5 msec intervals and the direction of inscription of the loops is indicated by the arrows The E point of each VCG trace is artificially exaggerated so that the origin of the loop may be clearly identified These loops were constructed by directly tracing the actual VCG s thus providing a precise reproduction of the actual VCG loops The P and T loops have been excluded

mitral valve into the outflow tract during systole (27 patients)

Left ventricular cineangiograms were obtained at a film speed of 60 frames per second in either the biplane or single plane mode with both right and left anterior oblique views Mitral insufficiency was assessed from the cineangiograms on a scale of 0 to 4+ Coronary artery and left ventricular cineangiograms were analyzed by two independent observers without prior knowledge of the ECG and VCG findings Since no quantitative method exists for estimating the size of the papillary muscles and since the heavy trabeculation prevented accurate measurement of ventricular wall thickness in these patients these data were estimated subjectively with cineangiographic analysis It is recognized that data obtained in this manner can be used only to make general comparisons

Standard 12 lead ECG s were recorded on all

papillary muscles and/or the left ventricular wall two patients with mild hypertrophy and two patients who were normal In the four patients with normal or mildly hypertrophied papillary muscles and ventricular walls three had no resting intraventricular gradient and one had a gradient of 11 mm Hg

The hemodynamic data of the two groups are compared in Table III There was no significant difference in maximum intraventricular gradient however left ventricular end diastolic pressure was significantly higher and cardiac output significantly lower in Group II Systolic and mean aortic pressures (not shown) were not significantly different in the two groups There was no significant correlation between maximum transverse plane voltage (VCG) and maximum intraventricular gradient in either patient group

Right dominance of the coronary artery system was seen in 29 of the 33 patients Two patients in Group I were found to have coronary anomalies in patient M Mc the circumflex artery rose from the initial portion of the right coronary artery and in patient [illegible] P both right and left coronary arteries arose from a common orifice in the right coronary sinus

Table III Hemodynamics of Groups I and II compared

	Rest gradient (mm. Hg)	*Maximum gradient (mm Hg)*	*LVEDP (mm Hg)*	*CO (L/min)*
Group I				
Mean	0	86	10	5 8
Range	0	(25-155)	(5 21)	(2 7 7 9)
S E M ±	0	8 7	1.3	0.3
Group II				
Mean	55	94	17	4 6
Range	(11 111)	(?3 100)	(7-40)	(3 0 6 7)
S E M ±	7 6	8.5	2 0	0 2
P<	0 001	NS	0 02	0 005

Rest gradient refers to intra entricular gradient without stimulation and was computed on [illegible] pat nts. Maximum gradient ref rs to the maximum intraventricular gradient obtained with or without stimul tion LVEDP = left ventricular end-diastolic pressure and CO = cardiac output For each pati nt group the mean range and stand [illegible] error of the mean (S E M) is given The two gro ps are compared using Student s t test for unpaired data and the P values are shown in the lower data line NS denotes th t the differ nces between gro ps were not signifi ant

Discussion

Brock[14] in 1957 first described outflow tract obstruction in both right and left ventricles however the ECG features of these patients were not described In 1960 Braunwald and associates reported 14 patients with idiopathic hypertrophic subaortic stenosis and noted the presence of large Q waves in the limb and precordial leads Estes and associates[6] reported 10 patients with idiopathic hypertrophic subaortic stenosis the initial forces were consistent with anterior infarction in four cases and with inferior infarction in two cases In five cases the ECG met criteria for left ventricular hypertrophy Although coronary arteriograms were performed in only one of these patients there was no history of preceding myocardial infarction Many other investigators have described patients with hypertrophic subaortic stenosis whose ECG s were compatible with anterior inferior or lateral myocardial infarction [8, 8, 11, 20, 23] Abnormal Q waves have been reported by a number of investigators and some have ascribed them to left ventricular septal hypertrophy [11, 22, 4] Wigle and Baron suggested that the diminution of the Q waves and tall precordial R waves by surgical incision in the septum supported asymmetrical hypertrophy as the cause Histologic studies in some patients with IHSS have revealed a bizarre pattern of hypertrophy and degeneration in the interventricular septum as compared to simple hypertrophy in left ventricular free wall [1, 2, 27] An alternate cause for the abnormal Q waves could be the cellular degeneration which may occur as the myopathic process progresses [1, 3]

Henry and associates[2] reported that in patients with asymmetrical septal hypertrophy posterolateral free wall hypertrophy is marked only in patients with outflow obstruction These observations are in accord with the cineangiographic data in our patients showing more marked hypertrophy of the papillary muscles and ventricular wall in patients with outflow obstruction at rest Group I patients (with no intraventricular gradient) may represent an earlier stage of asymmetric septal hypertrophy The disease process may spread in some patients to involve the entire septum causing malalignment of the papillary muscles and subsequent mitral insufficiency The presence of mitral insufficiency may potentiate hypertrophy of papillary muscles and left ventricular free wall A review of the previously reported patients in whom ECG and hemodynamic data are recorded reveals similar

Table II Hemodynamic and angiographic data in Group II patients

Pt	ECG VCG	Rest gradient (mm Hg)	Maximum gradient (mm Hg)	Post PVC	Ant MVM	Mitral Insuff	Ventricular wall	Papillary muscle
L C	LVH	65	99†	–	Yes	3†	Moderate	Moderate
G G	LVH	11	118†	Pos	Yes	0	Normal	Normal
F R	LVH	70	160†	Pos	Yes	3†	Severe	Severe
E S	LVH	60	60	Pos	Yes	3†	Severe	Severe
O C	LVH	100	100	Pos	Yes	4†	Severe	Severe
I T	LVH	0	36*	Pos	Yes	2†	Mild	Mild
C S	LVH	0	70†	Pos	Yes	3†	Mild	Mild
L M	LVH	83	83	–	Yes	2†	Severe	Severe
C B	LVH	0	76	Pos	Yes	0	Severe	Severe
M W	LVH	40	127†	Pos	Yes	2†	Severe	Severe
L W	LVH	47	47	Pos	Yes	3†	Severe	Severe
M T	LVH	0	150†	Pos	Yes	0	Severe	Severe
J B	LVH	13	72	Pos	Yes	0	Severe	Severe
V B	LVH	3[illegible]	145	Pos	Yes	2†	Moderate	Moderate
L G	LVH	0	97*	Neg	Yes	1†	Moderate	Mild
M F	LVH	111	111	–	Yes	3†	Severe	Severe
D G	LVH	0	152	Pos	Yes	0	Severe	Severe
K D	LVH AMI	83	83	Neg	Yes	1†	Moderate	Moderate
M B	LVH IMI	0	23	Pos	No	0	Normal	Normal
A H	LVH AMI IMI	48	100†	Pos	Yes	2†	Moderate	Moderate
M S	LVH AMI IMI	30	30	Pos	Yes	0	Mild	Moderate
J W	LVH AMI IMI	42	120†	Pos	Yes	1†	Moderate	Moderate

In column 2 the abbreviations are left ventricular hypertrophy (LVH) and anterior myocardial infarction (AMI) The remainder of the notations are described in the legend for Table I

verse plane maximum amplitude was 1 5 ± 0 1 mv (S E M) for Group I patients and 2 9 ± 0 4 mv (S E M) for Group II patients ($P < 0.002$)

Four representative examples of frontal and transverse vectors for patient Groups I and II are shown in Fig 1 In Group I patients R T and N K demonstrated inferior infarction The VCG s of patients M Mc and B P were normal In Group II, patients E S and G G have voltage and T loop criteria for LVH and in addition to LVH patients A H and M S met criteria for both AMI and IMI

Analysis of the cardiac catheterization data reveals striking differences between the two groups Group I patients had no resting intraventricular gradient although provocation with amyl nitrite or isoproterenol produced significant gradients in all patients (Table I) Four of 11 patients showed a post PVC decrease in arterial pulse pressure at rest and five additional patients developed this response after isoproterenol infusion None had angiographic evidence for mitral insufficiency In the 11 patients in whom mitral valve movement could be adequately visualized, six demonstrated abnormal movement of the anterior leaflet of the mitral valve into the outflow tract during ventricular systole The papillary muscles and ventricular wall were normal or only minimally hypertrophied in 10 of 11 Group I patients

In Group II, 18 of the 22 patients had either a resting intraventricular gradient and/or mitral insufficiency (Table II) In the seven patients without mitral insufficiency four had no resting gradient and three had resting gradients of 11 13 and 30 mm Hg In 21 patients anterior movement of the anterior mitral leaflet was demonstrated during ventricular systole In 15 of the 19 patients having PVC s during catheterization, a post PVC diminution of the arterial pulse at rest was seen and two additional patients demonstrated this finding during isoproterenol infusion Left ventricular cineangiograms revealed 18 patients with moderate to severe hypertrophy of either the

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17 Starr J W Wagner G E Behar V S Walston A and Greenfield J C Jr Improved vectorcardiographic criteria for the diagnosis of inferior myocardial infarction Circulation 49 829 1974
18 Brock R Functional obstruction of the left ventricle acquired aortic subvalvar stenosis Guys Hosp Rep 106 221 1957
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correlations as seen in our patients and lends support to our conclusions[6,11,19,1,25]

In the cases presented here the documentation of normal coronary arteries allows comparison of ECG and hemodynamic data without the complicating factor of previous ischemic myocardial damage The abnormal initial forces seen in IHSS may result from the dynamic interplay between bizarre cellular hypertrophy, cellular degeneration asymmetrical septal and free wall hypertrophy, and the subsequent altered myocardial geometry These data suggest that hemodynamic and anatomic characteristics may be predicted from the ECG and VCG in patients with IHSS The high correlation between ECG evidence of LVH and the presence of mitral insufficiency ventricular and papillary muscle hypertrophy may allow greater use of the ECG in the management of these patients

Summary

The ECG and Frank VCG were compared to the hemodynamic findings in 33 patients with idiopathic hypertrophic subaortic stenosis in whom cardiac catheterization had excluded concomitant valvular heart disease congenital heart disease or occlusive coronary artery disease The patients were divided into two groups according to the absence (Group I) or presence (Group II) of left ventricular hypertrophy on the ECG and/or VCG The 11 patients in Group I were found to have neither mitral insufficiency nor a resting left intraventricular gradient and only six patients in whom mitral valve movement was visualized demonstrated systolic anterior movement of the anterior leaflet The papillary muscles and left ventricular wall were either normal or only mildly hypertrophied in 10 of 11 Group I patients Group II (22 patients) demonstrated either a resting left intraventricular gradient and/or mitral insufficiency in 18 patients Twenty one of the 22 patients showed systolic anterior movement of the anterior leaflet of the mitral valve on cineangiogram and the papillary muscles and left ventricular wall were moderately to severely hypertrophied in 18 patients

These data suggest that specific hemodynamic and anatomic characteristics of hypertrophic subaortic stenosis may be predicted with reasonable accuracy from the ECG and VCG

The secretarial assistance of Mrs Brenda Haley and Mrs Rosa Ethridge is gratefully acknowledged The Department of Medical Illustration at the Durham Veterans Hospital rendered valuable support

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Abnormal motion of the mitral valve with pericardial effusion Pseudo-prolapse of the mitral valve

Jorge A Levisman, M D
Abdul S Abbasi, M D
Los Angeles Calif

Recently, the syndrome of the mid systolic click-late systolic murmur associated with prolapsing mitral leaflets has been increasingly recognized[1-4] This syndrome is not always benign, arrhythmias, sudden death, and bacterial endocarditis have been reported in these patients[5,6] Correct diagnosis of prolapse of the mitral valve is therefore essential Echocardiography has been found to be a reliable noninvasive technique in the diagnosis of the prolapsing mitral valve[4] The criterion currently accepted for its diagnosis is a posterior displacement of one or both mitral leaflets during systole below the closing point of the leaflets at the onset of ventricular systole the so called 'C' point (Fig 1) Instances of false positive diagnoses of this syndrome on echocardiography have not been reported This report describes cases in which a systolic posterior displacement of the mitral valve was the result of pericardial effusion

Methods

Echocardiograms were obtained with commercially available equipment using a 2 25 MHz 10 cm focus transducer with standard techniques described in the literature Eight patients with chronic large pericardial effusions were studied The echocardiograms were repeated in three after spontaneous resolution of the effusion and in four after pericardiocentesis Two patients had signs of tamponade The amount of fluid removed varied from 500 to 900 ml Physical examinations by at least two cardiologists were reviewed for evidence of systolic clicks and/or apical systolic murmurs Twenty five echocardiograms of patients with mild to moderate pericardial effusions where the mitral valve was well seen were also reviewed

Results

Seven of eight patients with chronic large pericardial effusion had echocardiograms showing an abnormal posterior motion of the mitral leaflet which started abruptly in midsystole with displacement below the level of the C point as described for typical mitral prolapse[4] (Fig 2) This abnormal systolic motion of the mitral valve was in the same direction and occurred simultaneously with a similar posterior motion of the anterior right ventricular wall interventricular septum and posterior left ventricular wall Mitral valve motion was perfectly normal in these patients after resolution of the effusion (Fig 3)

None of these patients had systolic clicks or apical systolic murmurs to suggest prolapsed mitral valve In the eighth patient with a large predominantly posterior, pericardial effusion mitral valve was normal as was motion of the anterior wall interventricular septum and posterior left ventricular wall Pericardial effusion was confirmed in this patient by serial chest x rays and cardiac blood pool scanning with radioactive technetium The echocardiograms of 25 patients with small to moderate pericardial effusion revealed either no abnormal motion of the mitral leaflets in systole or a slight late systolic posterior motion which never extended below the C point

From the Department of Medicine University of California School of Medicine Los Angeles Calif

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Reprint requests Jorge A Levisman M D University of California Medical Center Los Angeles Calif 90024

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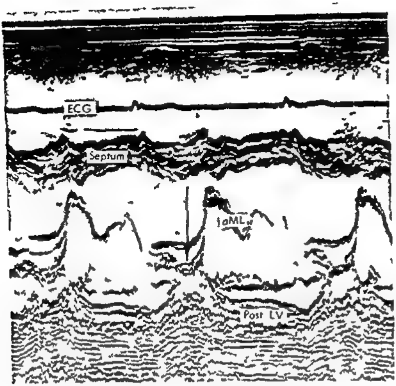

Fig 1 Echocardiogram of a prolapsed mitral valve The arrow indicates the abnormal posterior motion of the mitral leaflets during late systole *AML* anterior mitral leaflet *Post LV* posterior left ventricular wall

Discussion

In chronic large pericardial effusions the entire heart moves abnormally in synchronization with its contraction [4] It has been suggested that this is due to the absence of the restraining function of the pericardium since both of its layers are no longer in apposition The heart suspended by the great vessels then swings freely in the fluid As a consequence of this swinging there is an apparent abnormality of the systolic motion of the mitral valve which mimics the feature typically described for a prolapsing mitral valve We could not rule out the latter diagnosis clinically since the absence of auscultatory findings of the mid systolic click–late systolic murmur does not exclude the diagnosis of prolapsed valve However the picture of pseudoprolapse of the mitral valve should be suspected whenever abnormal systolic motion of the mitral leaflets is accompanied by a congruous motion of the anterior right ventricular wall interventricular septum and posterior left ventricular wall The exclusion of real prolapsing mitral valve is more definite with normalization of the systolic motion after resolution of the effusion The presence of a

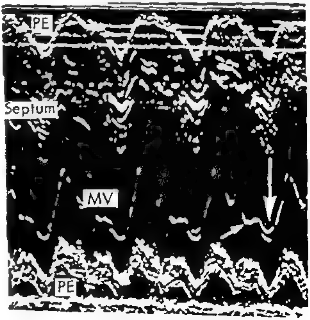

Fig 2 Echocardiogram of the "pseudoprolapse" of the mitral valve *PE* pericardial effusion *MV* Mitral valve The large arrow indicates the abnormal systolic motion of the valve The small arrow points to the "C" point Note the congruous motion of the anterior right ventricular wall interventricular septum, and posterior wall which is posterior at late systole

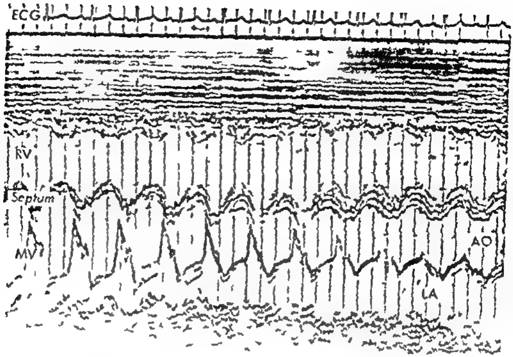

Fig 3 Echocardiogram of the same patient after a pericardiocentesis that yielded 525 ml The motion of the mitral valve is now normal

pseudoprolapse of the mitral valve suggests that the pericardial effusion is large while its absence favors a small to moderate effusion (25 cases)

One of our patients with a clinically large pericardial effusion did not show the motion of a pseudoprolapsed mitral valve ' In this case the echocardiogram showed a large posterior collection while anterior fluid was absent It is possible that this patient had anterior pericardial adhesions which restrained the heart preventing the abnormal swinging motion

Summary

The echocardiograms of seven patients with large pericardial effusions were found to show posterior motion of the mitral leaflets in systole as seen in prolapse of the mitral valve Repeat echocardiograms after resolution of the effusion revealed normal mitral valve motion None of the patients had clinical evidence of prolapsed mitral valve We postulate that a posterior swing of the heart within the pericardial fluid occurring in late systole causes posterior displacement of the mitral valve simulating a prolapsed valve

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Correlation of heart size with clinical and hemodynamic findings in patients with coronary artery disease

Agop Aintablian M D
Robert I Hamby M D
Jay Garsman M D
New Hyde Park Jamaica and Stony Brook N Y

Since the advent of coronary bypass surgery numerous patients with angina pectoris are subjected to cardiac catheterization and coronary angiography With improved surgical technique the mortality rate from coronary bypass surgery has been reduced from between 15 and 20 per cent to less than 1 per cent in selected cases Poor operative results and the high surgical mortality rate of patients subjected to coronary bypass surgery have been found to depend on the severity of coronary artery disease the number of previous myocardial infarctions[3] cardiomegaly [4] left ventricular dysfunction [1,4,5] elevated left ventricular end diastolic pressure [5] and diminished ejection fraction [6]

We reviewed 207 patients clinical hemodynamic and angiographic findings as well as the heart sizes from roentgenograms of the chest with the purpose of disclosing the correlation between the heart size and hemodynamic parameters in predicting from chest x rays and clinical findings which patients will be poor surgical risks for coronary bypass surgery

Material and methods

Clinical electrocardiographic (ECG) radiographic hemodynamic and angiographic findings of 207 consecutive patients were reviewed to evaluate the correlation of heart size and hemodynamic parameters Excluded from this study were patients with coronary artery disease who were catheterized primarily for conditions other than angina pectoris Also excluded were patients with angina pectoris who had coexisting mitral insufficiency ventricular septal defect or other valvular disease All patients were referred because of intractable angina pectoris Thirty four patients (16 per cent) had cardiomegaly and 173 patients (84 per cent) had normal size hearts Comparison of these two groups will be the basis of this report

On admission to the hospital all patients had a complete history and physical examination A history of myocardial infarction was accepted if documented by the referring doctor or if the patient had a prior hospitalization for at least 3 weeks for prolonged chest pain A history of congestive heart failure was based on a prior hospital admission for congestive heart failure or shortness of breath not associated with angina pectoris and requiring digitalis and/or diuretic therapy A diagnosis of hypertension required either a history of hypertensive therapy or a persistent diastolic pressure of 90 mm Hg or over when admitted for evaluation The ECG diagnosis of a myocardial infarction was based on accepted criteria[7] Radiologic evaluation and interpretation were performed by two different radiologists to define the presence or absence of cardiomegaly based on the criteria of definitely enlarged heart size defined by Norris and associates All patients had a glucose tolerance test the day prior to hemodynamic and angiographic evaluation An abnormal glucose tolerance was defined when the 2 hour blood sugar was over 120

From the Department of Medicine Cardiology Division and Department of Radiology Long Island Jewish Hillside Medical Center New Hyde Park Queens Hospital Center Affiliation Jamaica and the School of Medicine Health Sciences Center State University of New York at Stony Brook Stony Brook, N Y

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Reprint requests Agop Aintablian, M D Cardiology Division Long Island Jewish-Hillside Medical Center New Hyde Park N Y 11040

Table I Clinical profile of patients studied

	Normal size heart		Enlarged heart	
Number of patients	173		34	
Age (mean years ± 1 S D)	53 ± 9 1		53 ± 6 2	
Male/female	8/1		33/1	
Duration of angina pectoris (mean years ± 1 S D)	3 3 ± 2 9		4 6 ± 3 1	
	No	%	No	%
Myocardial infarction (by history)	95	52	25	73
Myocardial infarction (by ECG)	67	39*	22	65
Shortness of breath	17	10	4	12
Hypertension	56	32	11	32
Congestive heart failure (by history)	5	2 9	9	26*
Left ventricular hypertrophy (by ECG)	9	5	5	15
Abnormal glucose tolerance	121	70	17	50

Comparison between groups p < 0 001

mg per 100 ml for patients under 50 years of age and 140 mg per 100 ml or over for patients 50 years of age and older

Hemodynamic studies consisted of right and left heart procedures The majority of patients had a transseptal procedure as well Pressures were measured in all chambers of the heart and cardiac output was obtained by the direct Fick principle The normal left ventricular end diastolic pressure for this laboratory is 11 mm Hg or less The heart rate recorded during determination of cardiac output was divided into the latter to obtain the stroke volume This, divided by the ejection time, defined the mean systolic ejection rate index (milliliters per second per square meter) The normal mean systolic ejection rate for this laboratory is 151 ± 46 Left ventricular angiograms were obtained in the right anterior oblique projection by injecting 0 50 to 0 75 ml per kilograms of 90 per cent sodium meglumine diatrizoate into the left ventricle through either the retrograde or transseptal catheter Cineangiograms were taken with a 35 mm camera at 60 frames per second The x ray equipment utilized for this study included a dual field 6 inch 3000 gain 9 inch 6000 gain image intensifier (General Electric) with a 35 mm synchronous camera (Photomechanism), utilizing a grid control x ray tube When the left ventricular angiogram was completed a grid of known dimensions was positioned at the approximate location of the left ventricle and filmed to permit correction due to magnification After the completion of the left ventricular angiogram, selective coronary angiograms were performed in multiple projections using methods described by Sones and Shirey[9] or Judkins[10] Left ventricular volumes were obtained with the use of a modification of the area length method[11] and the regression equation derived by Herman and Bartle[11] The cine films were projected with a 35 mm projector (Vanguard Instrument Corp) on a ground glass screen The area of the left ventricular cavity was obtained with an electronic digitizer (Graf/Pen Science Accessories Corp) interfaced to a digital computer (Hewlett Packard) for calculating volumes The left ventricular end diastolic volume index and ejection fraction determined in 25 patients with normal left ventricles by this method were 69 ± 21 ml per square meter and 0 66 ± 12 respectively

The pattern of left ventricular contraction was determined by reviewing the superimposition of the end diastolic and end systolic silhouette and utilizing the descriptive terminology suggested by Herman and associates[12] Each of the three main coronary arteries was scored 0 to 6 as previously described[13] depending on the severity of involvement of that vessel, according to the criteria defined by Bruschke[14] The total coronary score for a patient was the sum of the scores of all three coronary arteries Involvement of the main left coronary was considered separately

Results

Clinical background As summarized in Table I out of 207 patients, 34 (16 per cent) had cardiomegaly and 173 (84 per cent) normal size hearts The male/female ratio was 8 in the group with normal heart size as compared to over 33 in patients with enlarged hearts The age ranges, duration of disease and history of myocardial infarction were similar There was no statistical difference in the incidence of shortness of breath, presence of hypertension, left ventricular hypertrophy, or abnormal glucose tolerance Patients with cardiomegaly had a significantly higher incidence of congestive heart failure (26 per cent) as compared to patients with normal heart size (2 9 per cent) ($P < 0.001$) They also had a higher incidence of ECG evidence of old myocardial

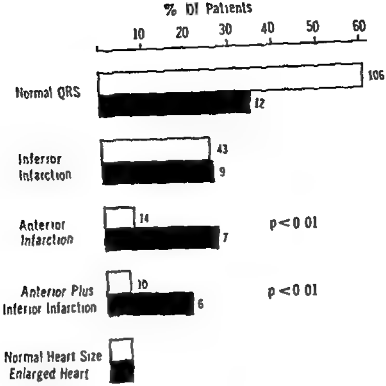

Fig 1 Frequency of cardiomegaly and normal sized heart in patients with normal QRS inferior anterior and anterior plus inferior infarction

infarction ($P < 0.01$) Anterior or combined inferior and anterior wall infarction were more frequent in patients with cardiomegaly than in patients with normal heart size ($P < 0.001$) (Fig 1)

Hemodynamic and angiographic study The left ventricular end-diastolic volumes were significantly higher and ejection fractions significantly lower in patients with cardiomegaly when compared to patients with normal heart size ($P < 0.001$) (Table II) End diastolic volumes were abnormally elevated in 6 per cent of patients with normal size hearts and in 41 per cent of patients with cardiomegaly The ejection fraction was abnormal in 15 per cent of patients with normal size hearts and in more than half of the patients with cardiomegaly The total coronary score was also higher in the cardiomegaly group ($P < 0.005$) As noted in Fig 2 single vessel disease was uncommon in patients with cardiomegaly whereas of those with normal heart size 24 per cent had single vessel disease Asynergy was noted in 55 per cent of patients with normal heart size and in 82 per cent of patients with cardiomegaly ($P < 0.001$)

Normal size heart with congestive heart failure Of 173 patients with normal heart size only five had documented congestive heart failure Four of these patients had ECG evidence of old myocardial infarction In these five patients the average ejection fraction was 0 49

Cardiomegaly with congestive heart failure Of 34 patients with enlarged heart nine had documented congestive heart failure Each of these patients had ECG evidence of old myocardial infarction and two patients had left anterior hemiblock and right bundle branch block. Hypertension was noted in four Left anterior descending coronary arteries were markedly stenosed or occluded in all nine patients (Table III)

The ejection fraction in each of these patients was 0 3 or less Akinesia of anterior wall or apical segment of the left ventricle was noted in five left ventricular aneurysm in one and generalized hypokinesia in three

Discussion

Cardiomegaly in patients with coronary artery disease has been attributed to hypertension alone[16] to coexisting hypertension and coronary artery disease[17] or to coronary artery sclerosis alone In this selected group of 207 patients

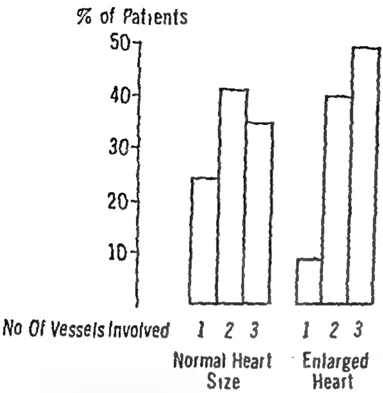

Fig 2 Frequency distribution of the number of vessels involved in the 173 patients with normal heart size and 34 patients with enlarged heart

Table II Hemodynamic and angiographic study

	Normal size heart		Enlarged heart	
	Mean ± 1 SD	%	Mean ± 1 SD	%
End-diastolic volume (ml /M)—per cent > 100 ml /M²	70 ± 20	[illegible]	99 ± 33 5	41*
Ejection fraction—per cent < 0 50	0 61 ± 0 12	15	0 46 ± 0 19	53
End diastolic pressure (mm Hg)—per cent > 11 mm Hg	12 1 ± 5 5	52	17 ± 8 3	65
Coronary score (mean ± 1 S D)	9 7 ± 3 2†		11 4 ± 3†	
	No	%	No	%
Asynergy	95	55	28	82

*Comparison between groups $P < 0.01$
†Comparison between groups $P < 0.05$

referred for evaluation of intractable angina pectoris we believe that cardiomegaly was caused predominantly by coronary artery disease since the incidence of hypertension was the same in patients with and without cardiomegaly The incidence of 16 per cent cardiomegaly in our study is compatible in value to those reported by Cohen and associates[18] (19 per cent) and by Masters[14] (21 per cent) Meanwhile in 200 patients with coronary artery disease, Parkinson reported an incidence of 64 per cent cardiomegaly Only 8 4 per cent was due to coronary disease the rest was attributed to hypertension alone

In the series of Bruschke and associates[3] congestive heart failure was noted in only 7 per cent out of 565 patients with angina pectoris as compared to 15 per cent in the present series The incidence of congestive heart failure in patients with normal heart size in Bruschke s series was 1 per cent, compared to 2 9 per cent in the present series In our patients cardiomegaly was associated with a high incidence of elevated end diastolic volume while elevated left ventricular end diastolic pressure was equally frequent in patients with normal and abnormal heart size There was no consistent relationship between the elevated end diastolic volume and end diastolic pressure confirming observations of Bristow and associates[1] in patients with coronary artery disease Our patients with cardiomegaly had extensive and severe coronary artery disease Double and triple coronary artery obstructions were more frequent in patients with cardiomegaly and also the total coronary score was higher in this group ($P < 0.05$) The incidence of asynergy was also higher in this group (82 per cent) as compared to patients with normal heart size (55 per cent)

Six patients with cardiomegaly had normal left ventricular contraction patterns none of them had ECG evidence of an old myocardial infarction, and only three had a history of hypertension It is difficult to explain the reason for cardiomegaly noted in these six patients with normal left ventriculograms In three patients hypertension alone or associated with coronary artery disease was the possible cause of cardiomegaly For the remaining three patients the possible explanations included (1) *Ischemic cardiomyopathy*—this seems unlikely since only two patients had a significantly elevated left ventricular end diastolic pressure In this entity [2, 22] all patients have significant asynergy and markedly diminished ejection fractions with

Table III Clinical hemodynamic and angiographic profile in patients with cardiomegaly and documented congestive heart failure*

Pt	Age/sex	MI H&NO	HBP	MI on ECG	EDV	EDP	EF	Asynergy	Coronary score	LAD score	MLC score	Other
1	56/M	+6	+	Anterior + inferior	146	[illegible]	0 18	Generalized hypokinesia	16/24	4	2	0
2	49/M	+2	+	Anterior + inferior	1[illegible]9	22	0 [illegible]3	AK anterior inferior	11	5	0	0
3	5[illegible]/M	+2	[illegible]	Anterior + inferior	127	19	0 30	AK apical, inferior	14	5	0	0
4	54/M	+1	0	Anterior	14[illegible]	3[illegible]	0.24	Generalized hypokinesia	15/24	[illegible]	3	[illegible]
5	51/M	0	+	Anterior	94	19	0 [illegible]8	Ant aneurysm AK inferior	7	3	0	[illegible]
6	59/M	+2	0	Anterior	185	28	0 17	AK anterior inferior	13	6	0	RBBB + LAH + 1 HB apical thrombus
7	54/M	+1	0	Anterior	147	3[illegible]	0 18	AK apical inferior	12	6	0	0
8	51/M	[illegible]	0	Inferior	129	11	0.27	AK anterior inferior	12	4	[illegible]	RBBB + LAH apical thrombus
9	57/M	+2	+	Inferior	90	22	0 22	Generalized hypokinesia	12	3	0	0

Abbreviations H&NO history and number of myocardial infarctions HBP hypertension MI myocardial infarction EDV end-diastolic volume EDP end-diastolic pressure EF ejection fraction AK akinesia LAD left anterior descending coronary artery MLC main left coronary artery RBBB right bundle branch block LAH left anterior hemiblock 1 HB first-degree heart block.

elevated left ventricular end diastolic pressure (2) *Misinterpretation of the heart size by chest x ray*—this is also unlikely as x rays were reviewed by two different radiologists (3) *Apparent but not real cardiomegaly*—comparative measurements of the heart size by quantitative angiogram compared to regular PA chest x rays revealed that the usual criteria for cardiomegaly by cardiac thoracic ratio are only 70 per cent accurate

Of 173 patients with normal heart size five had a history of documented congestive heart failure and ECG evidence of old myocardial infarction The left ventricular ejection fraction in this group was 0 49 Each of these patients had asynergy of the left ventricle with or without an elevated end diastolic pressure or end-diastolic volume Congestive heart failure in this group of patients most likely is due to localized asynergy of the left ventricle, rather than representing an early phase of stiff heart syndrome reported by Dodek and associates[25] According to these authors all patients not only had an ejection fraction of 0 49 values similar to those of our patients but all of them had elevated left ventricular end diastolic pressures

It is interesting to note that all nine patients with cardiomegaly and congestive heart failure had ejection fractions of 0 30 or less Left ventricular angiograms in this group showed asynergy of at least one wall of the left ventricle Three patients had generalized hypokinesia and one patient had aneurysm of the anterior wall of the left ventricle (Table III) All had significant left anterior descending artery stenosis ECG evidence of old myocardial infarction was present in nine Four however had combined anterior and inferior wall infarction Russell and associates[24] in the follow up of 25 patients with documented myocardial infarction noted cardiomegaly and congestive heart failure in six The ejection fraction in these six patients was less than 0 30 results similar to ours

These findings identify a group of patients with angina pectoris a history and ECG evidence of single or multiple myocardial infarction and documented congestive heart failure in whom chest x rays show cardiomegaly These patients form a relatively homogeneous group in whom the ejection fraction can be predicted at 0 30 or less before the cardiac catheterization and left ventricular angiogram The prognosis for survival

is poor in these patients, with or without coronary bypass surgery[27] The operative mortality rate in such patients is reported to vary between 12 5 and 43 per cent and left ventricular function did not improve at all or showed insignificant improvement postoperatively[4,5,30] For this reason, most authors do not advise surgical intervention in these patients[8,11] In the absence of clinical evidence of mitral regurgitation, ventricular septal defect or ventricular aneurysm, cardiac catheterization may not be necessary in these patients

Summary

The clinical hemodynamic and angiographic findings were correlated with the heart size in 207 patients with proved coronary artery disease

Cardiomegaly was noted in 34 patients and normal heart size in 173 In these two groups the patients age range duration of disease and history of myocardial infarction were similar There was no statistical difference in incidence of shortness of breath, hypertension left ventricular hypertrophy or abnormal glucose tolerance

Patients with cardiomegaly had a significantly higher incidence of congestive heart failure (26 per cent) as compared to patients with normal heart size (2 9 per cent) ($P < 0\,001$) Patients with enlarged heart presented a high incidence of anterior wall or multiple myocardial infarction (73 per cent) ($P < 0\,001$) The cardiomegaly group had a high incidence of elevated end diastolic volumes elevated end diastolic pressures, and diminished ejection fractions when compared to patients with normal heart size ($P < 0\,01$)

Double and triple coronary artery disease was more frequent in patients with cardiomegaly and total coronary score was also higher in this group ($P < 0\,005$) Asynergy was present in 55 per cent of patients with normal heart size but in 82 per cent of those with enlarged hearts ($P < 0\,01$)

The group of patients with cardiomegaly and documented congestive heart failure had ejection fractions less than 0 30 Cardiac catheterization is probably not advisable in these patients in the absence of associated significant mitral regurgitation ventricular septal defect, or ventricular aneurysm

We thank Dr Irwin Hoffman for his critical appraisal of this manuscript

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Association between clinical cardiac status, laboratory parameters, and digoxin usage

David H Huffman, M D
James W Crow, Ph D
Pertti Pentikainen, M D
Daniel L Azarnoff M D
Kansas City Kan and Mo

The cardiac glycosides are among the most effective drugs available for improving myocardial contractility Their use however, is not without hazard since a significant number of patients develop toxicity[1,2] Recent improvements in our knowledge of the pharmacology and therapeutic use of the digitalis glycosides should make our use of these drugs in patients more rational and decrease the number of toxic events[1,3] The development of the digoxin radioimmunoassay[4,5] has been particularly useful in this regard There have been a number of studies which have evaluated the relationship between the serum digoxin concentration and clinical evidence of digoxin intoxication[6-10] With the exception of one study,[10] all of these have demonstrated a significant positive relationship between the serum digoxin concentration and clinical evidence of glycoside intoxication

The present study was undertaken to evaluate the relationship between serum digoxin concentrations, other laboratory parameters and the clinical response of patients receiving digoxin In addition to defining a significant relationship between the serum digoxin concentration and cardiovascular response we have also determined a correlation between the clinical cardiac status and a number of routine laboratory tests

Methods

During the period of July 1971, to June 1973, the serum digoxin concentration was determined in over 1 200 patients admitted to the University of Kansas Medical Center From this group 143 patients who received a constant maintenance dose of digoxin for a minimum of 1 week were selected for this review All patients received digoxin (Burroughs Wellcome) during their hospitalization Each patient was seen in consultation by one of us at the time the drug level was obtained, however an extensive chart review was made at a later date by an independent observer who classified the patients without knowledge of the serum digoxin concentration

The patients were divided into four groups on the basis of clinical considerations The groups were as follows I, not toxic in congestive heart failure II not toxic not in congestive heart failure III possibly toxic, IV definitely toxic

The criteria of Beller and associates[11] were used for separating the patients into not toxic, 'possibly toxic,' and 'definitely toxic groups and were based in part on the electrocardiogram (ECG) The further division of the not toxic patients into Group I and II was based on the clinical status of the patient and the chest x ray The following laboratory data were recorded for each patient whenever available age sex, weight diagnosis blood urea nitrogen (*BUN*), creatinine creatinine clearance Na K , CL CO_2 serum

From the Clinical Pharmacology Toxicology Center Departments of Medicine and Pharmacology University of Kansas Medical Center and College of Health Sciences and Hospital Kansas City Kan and the Kansas City Veterans Administration Hospital Kansas City Mo

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Reprint requests Daniel L Azarnoff M D Clinical Pharmacology-Toxicology Center The University of Kansas Medical Center College of Health Sciences and Hospital Rainbow Blvd at 39th Kansas City Kan 66103

Table I Duncan s Multiple Range Test for significant digoxin parameters*

Variable	*F*	*df*	*Group*			
			I	*II*	*III*	*IV*
Weight (*Kg*)	3.60	3/142	72.7 ± 14.2†	65.3 ± 14.3	64.0 ± 15.1	60.7 ± 17.6
CRC (ml /min)	3.01	3/130	62.4 ± 31.4	60.9 ± 32.8	47.7 ± 30.3	41.5 ± 21.9
Dose (*mg*)	3.54	3/142	0.234 ± 0.10	0.260 ± 0.09	0.292 ± 0.08	0.316 ± 0.09
Level (*ng /ml*)	6.57	3/142	0.95 ± 0.52	1.49 ± 0.46	2.53 ± 0.64	3.32 ± 1.23
Dose/Kg (ng /kg)	6.245	3/142	0.003 ± 0.002	0.004 ± 0.002	0.005 ± 0.001	0.005 ± 0.001

*Any two means not underscored by the same line are significantly different at the 95 per cent level.
†Mean ± S D

glutamic oxaloacetic transaminase (SGOT) bilirubin alkaline phosphatase Ca lactic dehydrogenase (LDH) albumin globulin and T

The serum digoxin concentration was measured by the radioimmunoassay procedure of Smith and associates[5] as it is used in our laboratory [20] Venous blood was collected 6 to 8 hours after drug administration for determination of the serum concentration Digoxin assays were performed in duplicate within 48 hours of receiving the sample The specificity and sensitivity of the antibody used in this assay were similar to antibodies with high affinity for digoxin previously reported [21, 2]

Quality control was maintained by two internal standards (1 25 and 2 5 ng per milliliter) which were prepared in large batches and assayed each day together with the standard curve and the unknown samples The coefficient of variation of 30 consecutive independent assays of the internal standards was 4 8 per cent

Statistical Methods

An analysis of variance was performed to determine if a significant difference existed among the means of the four groups for each of the variables If there was a significant difference at the 95 per cent level of confidence it was further analyzed by Duncan s[23] Multiple Range Test as modified by Kramer[3] for unequal groups to determine which of the groups were different

Multiple regression analysis Patients with missing laboratory data for weight age creatinine BUN sodium potassium carbon dioxide chloride or SGOT were deleted 116 patients remained for the multiple regression analyses These patients were divided into three groups for this analysis subtherapeutic (Group I n = 27) therapeutic (Group II n = 57) and toxic (Groups III and IV n = 32) For this analysis the creatinine clearance which was missing for 46 patients was estimated from a nomogram [24]

Four stepwise regression analyses[25] were performed at the 95 per cent level of confidence (1) therapeutic vs subtherapeutic (2) therapeutic vs toxic (3) therapeutic vs subtherapeutic without consideration of the digoxin level and (4) therapeutic vs toxic without consideration of the digoxin level

Discriminant function analysis Two discriminant function analyses were obtained one for therapeutic vs subtherapeutic and the other for therapeutic vs toxic patients Those clinical and laboratory variables which absorbed the most variance in the multiple regression analysis guided the selection of those used in the discriminant function analyses A discrimination index I was calculated for each patient as a function of the independent variables selected for the discriminant analysis

$$I_j = \sum_{i=1}^{n} c_i X_{ji}$$

where c_i is the discriminant function coefficient and X_{ji} the value(s) of the independent variable(s) for the j^{th} patient

The patients were ranked in descending order by their calculated index A discrimination value was selected which minimized the total number of classification errors Patients with a discrimination index higher than this discrimination value were assigned to the therapeutic group Those patients with a discrimination index lower than the discrimination value were assigned to either the subtherapeutic group or the toxic group depending on which groups were part of

Table II Discriminant analysis therapeutic vs toxic

Run No	Variable included	Errors* Type I	Errors* Type II	Discriminant function coefficients	Discrimination value
1	Level	3	5	−0 03208	−0 07058
[illegible]	Dose	9	–	−0 06649	−0 01662
3	Dose/Kg	13	13	−4 12271	−0 01874
4	Level	4	5	−0 03151	−0 07620
	Dose			−0 02751	
[illegible]	Level	3	6	−0 03154	−0 07394
	Dose/Kg			−1 11019	
[illegible]	Level	3	[illegible]	−0 03162	−0 06679
	CRC			0 00006	
7	Level	4	5	−0 03026	−0 07201
	Dose			−0 04395	
	CRC			0 00012	
8	Level	2	8	−0 03540	−0 07748
	Bun			0 00033	
	CRC			0 00031	
	Wt			−0 00030	
9	Dose	10	10	−0 10767	−0 01313
	CRC			[illegible] 00033	
10	Dose/Kg	9	14	−5.25804	−0 01231
	CRC			0 00027	

*Misclassifications Type I misclassified a therapeutic patient as a toxic patient Type II misclassified a toxic patient as a therapeutic patient.

the analysis Two types of classification errors were possible In the analysis between thera peutic and toxic patients a Type I error resulted when a toxic patient was misclassified as thera peutic whereas a type II error resulted if a patient in the therapeutic group was misclassified as toxic All statistical analyses were performed by an IBM 370 model 145 computer

Results

Significant differences between the means of the four groups at the 95 per cent level of confidence were found among the four clinically different groups for the following variables digoxin level, dose per kilogram body weight, dose, and creatinine clearance The results of the Duncan s Multiple Range test for differences between groups are presented in Table I The digoxin level had the highest F value (67 57) The mean digoxin level of each group was significantly different from the other three groups Although there was a progressive decrease in the creatinine clearance from Groups I to IV, the differences among Groups I II and III and between Groups III and IV were not significant However, the creatinine clearance was significantly lower in the 'toxic groups (III and IV) than in 'not toxic' Groups I and II Patients in Group I weighed significantly more than did all other patients (Groups II III, and IV)

The absolute digoxin maintenance dose as well as the dose per kilogram increased from Group I to Group IV The not toxic groups (I and II) received significantly less digoxin than those in Group IV Four stepwise multiple regression analyses were performed In comparing thera peutic and subtherapeutic, the regression equa tion absorbed 13 7 per cent of the variance (R^2) when drug level was not considered whereas 29 5 per cent was absorbed when level was included This same trend was more evident between the therapeutic and toxic groups when the digoxin level was included in the regression analysis 55 5 per cent of the variance was absorbed Of this 55 5 per cent, 50 per cent of the variance was absorbed by the digoxin level alone and only an additional 5 per cent by adding 12 other variables In con trast, when the digoxin level was not included only 24 5 per cent of the variance was absorbed

When level is considered in both therapeutic vs toxic and therapeutic vs subtherapeutic regression analyses it carries the greatest weight

in the regression equation (i e highest b value) Because level is so predictive 13 variables* in the therapeutic vs toxic and 10† in the therapeutic vs subtherapeutic are included in the regression equation as opposed to the comparisons when level is excluded Only 7‡ and 5§ variables are included at the 95 per cent level in the latter two comparisons without the digoxin level There is approximately a 1 5 to 2 0 fold increase in the correlation coefficient (R) when level is considered

If level enters the regression equation creatinine clearance BUN and dose weigh heavily in the therapeutic vs toxic groups whereas patient weight enters significantly in the therapeutic vs subtherapeutic regression equation This trend was suggested by Duncan s Multiple Range Study (Table I)

In Table II the results of the discrimination analysis are given for comparison of therapeutic vs toxic patients for 10 different combinations of the variables which contributed most to the multiple regression analysis The digoxin level alone was the best predictor of the clinical response of the patient This table can be used for determining the appropriate classification of a patient into either the therapeutic or toxic group by multiplying the independent variable(s) (e g level or dose) by the appropriate discrimination function coefficient(s) If the determined discrimination index is algebraically greater than the discrimination value in the table the patient can be appropriately considered in the therapeutic group If it is less than the discrimination value the patient is in the toxic or possibly toxic group For example using the values for run 1 if the patient s steady state digoxin level is 1 4 ng per milliliter the discrimination value is 1 4 × (−0 03208) = −0 0448 which is greater than −0 07058 and he is placed in the therapeutic group

Comment

Our observations confirm the majority of previous studies demonstrating that the utility of the serum digoxin concentration in evaluating the clinical response to digoxin has been established Evidence has been reported[27, 28] that the availability of the serum digoxin concentration is associated with a 50 per cent reduction of clinical digoxin intoxication although digoxin continues to be a major cause of drug toxicity[29, 31] From the analyses of the data reported here we determined that factors in addition to serum digoxin concentration were of value in assessing the relationships between digoxin therapy and clinical cardiac status A positive correlation was found between the clinical cardiac status of the patient and the serum digoxin concentration digoxin dose body weight and the creatinine clearance Although other factors contributed to the categorization of patients into therapeutic or toxic groups differences among the means for these factors were not significantly different

Previous studies relating serum digoxin concentrations to patient response have compared not toxic with either toxic patients or potentially toxic patients We have attempted to define a therapeutic and subtherapeutic group by dividing the not toxic patients into those with and those without congestive heart failure and to determine the importance of other factors such as renal function Although the lowest mean digoxin concentration occurred in the subtherapeutic group (I) one cannot assume that the poor response was due only to inadequate glycoside levels since other factors such as excess dietary sodium intake inadequate diuretic therapy the presence of valvular lesions or infiltrative cardiomyopathies may have a greater effect on cardiac function than the increased inotropic effect induced by digitalis Another factor commonly implicated in therapeutic failures with digoxin therapy is inadequate patient compliance[32] The patients in the present study were hospitalized and had received a maintenance dose of digoxin for at least 7 days With these reservations the therapeutic range predicted from discrimination

*The variables in the order they entered the regression equation comparing therapeutic and toxic groups (digoxin level included) were digoxin level, BUN creatinine clearance potassium chloride age CO creatinine dose dose per kilogram, and sodium

†The variables in the order they entered the regression equation comparing therapeutic and subtherapeutic groups (digoxin level included) were digoxin level, weight age, creatinine BUN SGOT sodium, chloride creatinine clearance and dose per kilogram

‡The variables in the order they entered the regression equation comparing therapeutic and toxic groups (digoxin level not included) were dose per kilogram, creatinine clearance dose creatinine BUN potassium and sodium

§The variables in the order they entered the regression equation comparing therapeutic and subtherapeutic groups (digoxin level not included) were weight, chloride age SGOT and sodium

function analyses is 1 0 to 2 2 ng per milliliter at 6 to 8 hours following a dose and is consistent with previously reported values[31]

A smaller dose, decreased absorption of digoxin in the presence of congestive heart failure, and/or an increased distribution volume for digoxin in these patients could explain the reduced serum digoxin concentration in Group I Although the mean digoxin dose was less in Group I than in Group II, the difference was not statistically significant Except to state that the patients were receiving a relatively bioavailable digoxin product we do not know whether digoxin absorption is decreased in congestive heart failure The patients in Group I were significantly heavier than the patients in the other three groups This is not surprising since most of this group had excess fluid which, perhaps is associated with an increased volume of distribution for digoxin

The discriminant function analysis based on level alone resulted in the fewest classification errors (8/89) It is interesting that where the analysis was based on dose alone one additional total error occurred (9/89) and all misclassifications were Type I errors Digoxin dose was the best in minimizing Type II error It can be argued that the Type II error which consists of the misclassification of a toxic patient as therapeutic is a more serious error

Of the three single independent variables level, dose and dose per kilogram, dose per kilogram was a significantly poorer predictor (in terms of total misclassifications) of both subtherapeutic and toxic patients Level was the best predictor, with dose being intermediate in both cases When classifying toxic patients the inclusion of level with combinations of other laboratory variables had no better predicting power than did level alone When level was deleted from the discrimination function of toxic patients the total number of errors is increased twofold as reflected in the dose, creatinine clearance and dose per kilogram, creatinine clearance studies (Table II)

A discriminant function analysis comparing therapeutic and subtherapeutic patients was less encouraging than the comparison of therapeutic and toxic patients The minimum number of errors made in classifying subtherapeutic was noticeably higher (20 per cent) than those in the toxic study (10 per cent) Also there was less clustering of the misclassifications in the subtherapeutic study leading to a high degree of error scattering This lack of predictive power may be reflecting a lack of patient data homogeneity within Group I The discrimination function for patient weight and level predicted better than the other variables in the subtherapeutic group as was suggested by the results of Duncan s Multiple Range test The principle of optimization used in discriminant analysis may give a biased overestimate of the reliability of the method Therefore if applied to another group of patients it may produce a higher rate of misclassification errors than were determined in this study

In the prospective study of Beller and associates,[13] decreased renal function in the toxic groups compared with therapeutic patients was the most important reason for digoxin intoxication There were no differences in the dose of digoxin in this study While renal function is an important factor in our study, it is apparent that the digoxin dose is also an important factor in the development of digoxin intoxication

There has been recent enthusiasm for the use of computer assisted programs to advise physicians on digoxin dosage regimens[34] These programs use pharmacokinetic information and have been shown to decrease the incidence of toxicity[31] However recent studies[36] indicate that the initial enthusiasm for these programs has abated It appears that a less expensive and more reliable way to evaluate digoxin therapy is to determine the serum digoxin concentration Since there is an overlap between the serum digoxin concentrations for patients in the various groups and since there are other factors such as age[37] thyroid status[38] acidosis hypokalemia hypoxia etc, which are all important determinants of the response to digoxin in the individual patient clinical judgment remains an essential factor in determining appropriate therapy with digoxin

The digoxin serum levels should not be determined routinely in every patient who receives digoxin particularly when adequate therapeutic benefit has been obtained and there is no evidence of digoxin toxicity However of the 15 per cent of patients taking digitalis on admission to a large hospital, 23 per cent were found to be definitely digitalis toxic by serial ECG[13] Incidences of digitalis toxicity from 10 to 21 per cent have also been reported in other recent studies[27, 39] Unfortunately, most of the symptoms and arrhythmias

suggestive of digitalis intoxication can also be caused by the cardiac dysfunction per se Physicians even after years of clinical experience cannot always discriminate between the two Other problems also exist Twenty five of 323 patients in a study were found to have zero digoxin blood levels even through they were supposedly taking their medication regularly[30] Patient compliance to digitalis dosage regimens[3] bioavailability drug interactions and physiologic abnormalities (malabsorption increased motility) can be detected by blood levels The use of digoxin blood levels has reduced digitalis toxicity significantly[3 28]

The clinician will find the serum digoxin level useful in deciding (1) if the patient is taking the glycoside regularly, (2) if bioavailability problems exist with the dosage form and (3) if an arrhythmia is due to the glycoside or intrinsic heart disease The level is also useful in a patient for whom an adequate history cannot be obtained when the physician wishes to know whether the patient is receiving digoxin or digitoxin and to determine whether the patient can be given more than the maintenance dose

The serum digoxin determination correlates well with the therapeutic and toxic responses of patients and serves a useful purpose in controlling digitalis therapy

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function analyses is 1.0 to 2.2 ng. per milliliter at 6 to 8 hours following a dose and is consistent with previously reported values.[11]

A smaller dose, decreased absorption of digoxin in the presence of congestive heart failure and/or an increased distribution volume for digoxin in these patients could explain the reduced serum digoxin concentration in Group I. Although the mean digoxin dose was less in Group I than in Group II, the difference was not statistically significant. Except to state that the patients were receiving a relatively bioavailable digoxin product, we do not know whether digoxin absorption is decreased in congestive heart failure. The patients in Group I were significantly heavier than the patients in the other three groups. This is not surprising since most of this group had excess fluid which, perhaps, is associated with an increased volume of distribution for digoxin.

The discriminant function analysis based on level alone resulted in the fewest classification errors (8/89). It is interesting that where the analysis was based on dose alone, one additional total error occurred (9/89) and all misclassifications were Type I errors. Digoxin dose was the best in minimizing Type II error. It can be argued that the Type II error which consists of the misclassification of a toxic patient as therapeutic is a more serious error.

Of the three single independent variables, level, dose, and dose per kilogram, dose per kilogram was a significantly poorer predictor (in terms of total misclassifications) of both subtherapeutic and toxic patients. Level was the best predictor, with dose being intermediate in both cases. When classifying toxic patients the inclusion of level with combinations of other laboratory variables had no better predicting power than did level alone. When level was deleted from the discrimination function of toxic patients the total number of errors is increased twofold as reflected in the dose, creatinine clearance, and dose per kilogram, creatinine clearance studies (Table II).

A discriminant function analysis comparing therapeutic and subtherapeutic patients was less encouraging than the comparison of therapeutic and toxic patients. The minimum number of errors made in classifying subtherapeutic was noticeably higher (20 per cent) than those in the toxic study (10 per cent). Also, there was less clustering of the misclassifications in the subtherapeutic study leading to a high degree of error scattering. This lack of predictive power may be reflecting a lack of patient data homogeneity within Group I. The discrimination function for patient weight and level predicted better than the other variables in the subtherapeutic group as was suggested by the results of Duncan's Multiple Range test. The principle of optimization used in discriminant analysis may give a biased overestimate of the reliability of the method. Therefore, if applied to another group of patients, it may produce a higher rate of misclassification errors than were determined in this study.

In the prospective study of Beller and associates,[13] decreased renal function in the toxic groups compared with therapeutic patients was the most important reason for digoxin intoxication. There were no differences in the dose of digoxin in this study. While renal function is an important factor in our study, it is apparent that the digoxin dose is also an important factor in the development of digoxin intoxication.

There has been recent enthusiasm for the use of computer assisted programs to advise physicians on digoxin dosage regimens.[14] These programs use pharmacokinetic information and have been shown to decrease the incidence of toxicity. However, recent studies[16] indicate that the initial enthusiasm for these programs has abated. It appears that a less expensive and more reliable way to evaluate digoxin therapy is to determine the serum digoxin concentration. Since there is an overlap between the serum digoxin concentrations for patients in the various groups and since there are other factors such as age,[17] thyroid status,[18] acidosis, hypokalemia, hypoxia, etc., which are all important determinants of the response to digoxin in the individual patient, clinical judgment remains an essential factor in determining appropriate therapy with digoxin.

The digoxin serum levels should not be determined routinely in every patient who receives digoxin, particularly when adequate therapeutic benefit has been obtained and there is no evidence of digoxin toxicity. However, of the 15 per cent of patients taking digitalis on admission to a large hospital, 23 per cent were found to be definitely digitalis toxic by serial ECG.[13] Incidences of digitalis toxicity from 10 to 21 per cent have also been reported in other recent studies.[27, 39] Unfortunately, most of the symptoms and arrhythmias

suggestive of digitalis intoxication can also be caused by the cardiac dysfunction per se Physicians even after years of clinical experience cannot always discriminate between the two Other problems also exist Twenty five of 323 patients in a study were found to have zero digoxin blood levels even through they were supposedly taking their medication regularly [8] Patient compliance to digitalis dosage regimens [23] bioavailability drug interactions and physiologic abnormalities (malabsorption increased motility) can be detected by blood levels The use of digoxin blood levels has reduced digitalis toxicity significantly [27, 28]

The clinician will find the serum digoxin level useful in deciding (1) if the patient is taking the glycoside regularly (2) if bioavailability problems exist with the dosage form and (3) if an arrhythmia is due to the glycoside or intrinsic heart disease The level is also useful in a patient for whom an adequate history cannot be obtained when the physician wishes to know whether the patient is receiving digoxin or digitoxin and to determine whether the patient can be given more than the maintenance dose

The serum digoxin determination correlates well with the therapeutic and toxic responses of patients and serves a useful purpose in controlling digitalis therapy

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Clinical study on the flow murmurs at the defect area of atrial septal defect by means of intracardiac phonocardiography

Tadashi Kambe M D
Norio Hibi M D
Hisao Ito M D
Takemi Arakawa M D
Kinya Nishimura M D
Hanako Ishihara M D
Arata Miwa M D
Hisao Tada M D
Nagoya Japan

The introduction of intracardiac phonocardiography by Yamakawa and associates in 1953 marked an epoch in the history of phonocardiography and led to a better understanding of the genesis and transmission of cardiac murmurs

The method of auscultation which we use in practice at the chest surface is not necessarily the correct reflection of sounds or vibratory phenomena in the cardiac chambers or great vessels Therefore since the last century various methods have been developed to evaluate heart murmurs as close to the cardiac chambers as possible Richardson and Hoffman first attempted auscultation via the esophagus route and recent advances in cardiac surgery have made possible epicardial auscultation from the heart surface

As the next step of progress many authors have tried intracardiac phonocardiography for the analysis of unknown intracardiac events

With regard to the intracavitary murmurs of atrial septal defect (ASD) there have been a wide variety of documents [1] since the introduction of intracardiac phonocardiography Attention has been paid mostly to the systolic murmur in the pulmonary artery however and the analysis of flow murmurs through the atrial septal defect still remains to be solved

Recently Somerville and Resnekov [2] reported an immediate diastolic murmur in atrioventricular defects and an early diastolic murmur was described by Wennevold [3] in atrial septal defects In addition the v murmur designated by Sakamoto and associates [4] has given rise to further investigation of flow murmurs at the defect area

The purposes of this article are the phasic analysis of flow murmurs of atrial septal defect by means of intracardiac phonocardiography and comments on the mechanism of production of these bruits from the hemodynamic standpoint

Material and methods

In order to study the flow murmurs at the defect area of atrial septal defect right heart catheterization was performed on 57 patients admitted to the Nagoya University Hospital for precise examination of heart with a double lumen phonocatheter of A E L * Model 192 at the tip of which barium titanate was mounted Findings are listed in Table I The diagnosis was confirmed with cardiac catheterization and angiocardiography in all cases and finally proved

From th Third Departm t of Internal Medicine Nag ya Un ersity School of Medicine Tsurumai-cho 65 Showa ku Nagoya Japan

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Reprint requests Tadashi K mbe M D Th rd Departm nt of Internal Medicine N g y Un versity School of Med cine T ruma cho 65 Showa ku N goy J pan.

*A.E.L. (American Electric Laboratories Inc) P O Box 55 La s-dale Pa. 19446

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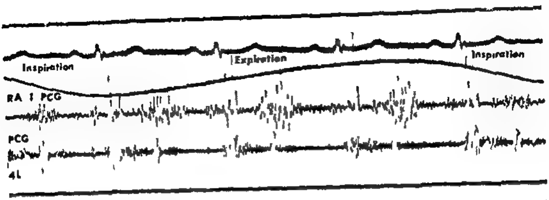

Fig 2 Influence of respiration on v murmur in a 21 year-old woman (K M) The v murmur augments in intensity on expiration and diminishes on inspiration *4L* = the fourth left intercostal space

responsible for production of the continuous bruit moreover pressure gradient between left and right atria greatly contributes to the formation of the shunt

No v murmur was noted in a cyanotic patient who had atrial septal defect with moderate valvular pulmonic stenosis reversed shunt is presumably not related to the continuous murmur In addition there was no significant correlation between the presence of v murmur and the amount of left to right shunt The pitch of the murmur ranged from low to medium frequency in most cases and it was rarely detected at the chest surface

Fig 2 shows the influence of respiration on v murmur simultaneous registration of respiration curve and intracardiac and external phonocardiograms on a 21 year old woman (K M) indicated that the continuous murmur augments with expiration and diminishes with inspiration The same tendency was found in all nine patients who were studied with regard to the effects of respiration

During exploration within the right atrium at the septal area with phonocatheters an early diastolic murmur was found at times at a slightly different site of the right atrium in the same patients who indicated v murmur It was thought to be not an independent murmur but an incomplete form of v murmur because of synchronous alteration with the atrial v wave It should be differentiated from mid diastolic murmur

Identification of the continuous murmur in the right atrium leads to the diagnosis of atrial septal defect in the absence of anomalous pulmonary venous drainage returning into the right atrium which also produces the murmur Consequently it is concluded that v murmur is essentially

Table II Incidence of v murmur

Diagnosis	*No of cases* +	–
Secundum type		
ASD	27	11
ASD + PS	2	4
ASD + APVD	2	1
ASD + PLSVC	1	0
Total	32	16
Primum type	1	3
Probe patent foramen ovale	0	5

+ = presence of murmur – = absence of v murmur

continuous extending from systole to diastole crescendo-decrescendo in configuration of low to medium frequency and best recorded at the septal area of the atrial septal defect

Mid diastolic murmur During investigation within the right atrium for detection of continuous murmur a mid diastolic murmur was encountered in four cases of secundum type the diagnosis of which was confirmed by surgical intervention. This is thought to be another murmur due to flow through the defects since it has no relation to v wave of the right atrium but is localized between v and a waves in the atrial pressure tracing Therefore the mid diastolic murmur at the septal area is an independent entity from v murmur and it also augments on expiration similar to the latter Furthermore the pitch of the diastolic murmur was of low to medium frequency in all cases

Fig 3 shows an example of mid diastolic murmur in the right atrium of a 24 year old man (M K) the same patient as described in Fig 1

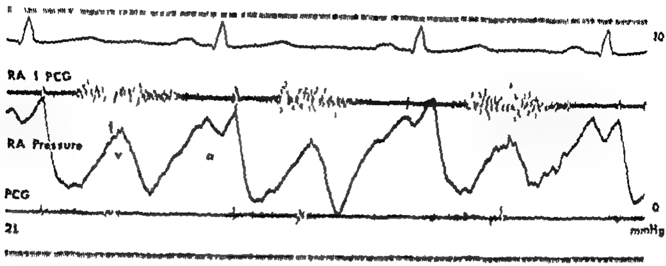

Fig 1 An example of v murmur (arrow) of secundum type in a 24 year old man (M K) It is recorded at the septal area in the right atrium essentially continuous crescendo decrescendo in configuration extending from late systole to diastole and closely related to the atrial v wave *RA* = right atrium *I PCG* = intracardiac phonocardiogram *PCG* = external phonocardiogram *2L* = the second left intercostal space

Table I Types of atrial septal defect

Diagnosis	*No of cases*
Secundum type	
ASD	38
ASD + PS	6
ASD + APVD	3
ASD + PLSVC	1
Total	48
Primum type	4
Probe patent foramen ovale	5

ASD = *atrial septal defect PS* = *pulmonic stenosis APVD* = *anomalous pulmonary venous drainage PLSVC* = *persistent left superior vena cava*

by heart surgery in 40 patients of the secundum type

Insertion of a phonocatheter into the right atrium was performed with the use of local anesthesia under fluoroscopic control via the left axillary vein, except in three patients who were examined through the right femoral vein The intracavitary phonocardiograms were obtained with great care at the atrial septum the tricuspid area, and the upper portion of the right atrium The left atrium was also explored in 14 cases of the secundum type and two of the primum type

In the majority of cases, simultaneous recording of intracardiac and external phonocardiograms and intra atrial pressure was made with the Polygraph of Fukuda denshi, EMR 100R and the photographic recorder of Sanei sokki 100A type In addition to the pressure transducer of strain gauge type TM 1, the contact microphone of Fukuda-denshi, MA 250 or PM 1, and the preamplifier, RE 1, were used for the registration of external phonocardiogram and respiration curves respectively The paper speed was 100 mm per second in the majority of cases

Results

In this study we classified the flow murmurs at the defect area of the right atrium into three patterns (1) v murmur (2) mid diastolic murmur, and (3) atriosystolic murmur

The v murmur Fig 1 shows an example of v murmur in a 24 year old man (M K) Simultaneous recordings were made of intracardiac phonocardiogram of the right atrium (RA I PCG) external phonocardiogram (PCG) and right atrial pressure and a continuous murmur was recognized at the defect area of the right atrium The murmur was thought to be equivalent to the v murmur designated by Sakamoto since it is essentially continuous, extending from late systole to diastole, crescendo decrescendo in configuration, and closely related to the atrial v wave

The incidence of v murmur is shown in Table II, it was recorded in 32 out of 48 cases (66 6 per cent) of secundum type and one of primum type but not observed in probe patent foramen ovale

Blood flow through the defect due to left to right shunt is considered to be the factor most

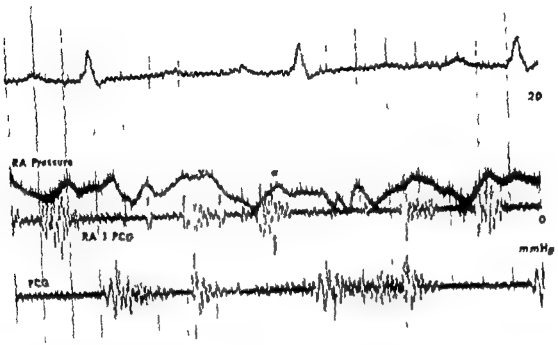

Fig 5 An atriosystolic murmur (arrow) in a 21 year-old woman (T O) of secundum type It is observed at the defect area in the right atrium coincident with atrial a wave and located prior to the first sound

Table III Incidence of atriosystolic murmur

Diagnosis	No of cases +	No of cases −
Secundum type		
ASD	13	25
ASD + PS	2	4
ASD + APVD	1	2
ASD + PLSVC	1	0
Total	17	31
Primum type	1	3
Probe patent foramen ovale	0	5

+ = presence of atriosystolic murmur − = absence of atriosystolic murmur

medium frequency similar to other flow murmurs

Fig 5 indicates an atriosystolic murmur in the right atrium of a 21 year old woman (T O) with atrial septal defect of secundum type the intracardiac and external phonocardiograms were recorded simultaneously with right atrial pressure demonstrating that the atriosystolic murmur was localized at the septal area of the right atrium and occurred in accordance with atrial a wave The ratio of pulmonic to systemic flow was 1 3

This murmur was observed in 17 out of 48 patients (35 4 per cent) of secundum type and one of primum type but not recorded in probe patent foramen ovale (see Table III)

The pressure gradient between a waves of both atria was thought to be the most likely mechanism for the production of atriosystolic murmur due to shunt flow through the defect In addition there was no significant correlation between the existence of atriosystolic murmur and the ratio of left to right shunt It may occur concomitantly with v murmur Atrial fibrillation leads to the disappearance of atriosystolic murmur Another atriosystolic murmur also exists in the inflow tract of the right ventricle due to relative tricuspid stenosis

Discussion

For more than 20 years intracardiac phonocardiography has been used to localize cardiac murmurs and has greatly contributed to improvement of clinical diagnosis Since the introduction of intracavitary auscultation there have been a wide variety of controversies over the genesis of flow murmurs across the atrial septal defects

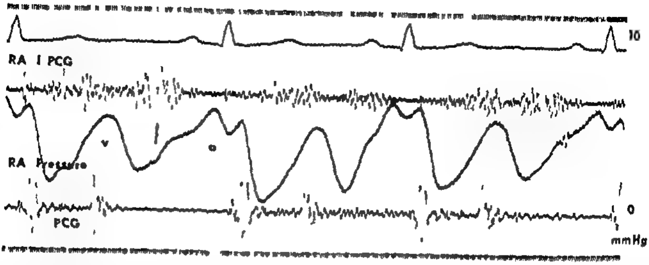

Fig 3 A mid-diastolic murmur in the right atrium (arrow) of the patient shown in Fig 1 The diastolic bruit is registered after v murmur and localized between atrial v and a waves It is thought to be an independent entity from v murmur and regarded as another murmur due to shunt flow through the defect because it has no relation to v wave In addition it is different in localization from the mid diastolic murmur due to relative tricuspid stenosis in the right ventricle

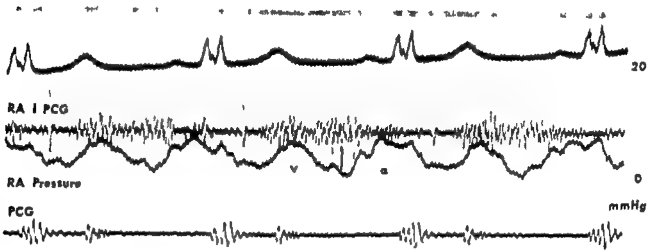

Fig 4 Another example of mid diastolic murmur in a 15 year old boy diagnosed as atrial septal defect of secundum type Low pitched mid diastolic murmur is demonstrated in the right atrium as shown by the arrow being separated from v murmur

The intracavitary phonocardiogram reveals that the mid diastolic murmur is recorded after v murmur and not coincident with the atrial v wave M K s condition was diagnosed as atrial septal defect of secundum type, he was proved by surgical intervention to be free of other lesions The ratio of pulmonic to systemic flow was 1 4

Fig 4 shows mid diastolic murmur in a 15 year old boy (T G), with isolated atrial septal defect of secundum type, who underwent open heart surgery The ratio of pulmonic to systemic flow was 5 1 The defect was oval in shape 3 by 2 cm In the intracardiac phonocardiogram, the mid diastolic murmur was also registered at the septal area being separated from v murmur

In general sufficient time interval between atrial v and a waves is necessary for the production of the mid diastolic murmur and tachycardia should be avoided during heart catheterization Moreover, it is of much interest that the mid diastolic murmur due to shunt flow across the defect is completely different in localization from that of relative tricuspid stenosis, which is usually detected in the inflow tract of the right ventricle of atrial septal defect

It is of our opinion that the mid diastolic murmur across the defect should be regarded as an independent entity separate from v murmur

Atriosystolic murmur This murmur is closely related to atrial a wave due to atrial contraction, and it is located in the presystolic phase prior to the first sound The pitch ranges from low to

recording of the respiration curve with the intra cardiac phonocardiogram which we have shown in this paper It is of interest that the mid diastolic murmur also augmented on expiration similar to v murmur

The third flow murmur at the defect is atriosystolic murmur which is closely related to atrial a wave However it should not be confused with the atriosystolic murmur due to relative tricuspid stenosis in the inflow tract of the right ventricle

In general intracardiac phonocardiography is most useful to localize cardiac murmurs and sounds A major advantage of intracardiac phonocardiography is that it may detect even a small eddy not audible as a murmur on the chest surface However this method has its limitations it may produce an artificial eddy in the heart chambers in addition to already existing murmurs Moreover a positional gap may occur between the shunt flow and the axis of sensitive element

In our experience when the catheter was floating in the cardiac chambers there were not so many artifacts during the phono catheterization of the right heart except on withdrawal of the phonocatheter from the pulmonary artery into the right ventricle whereby the tip of the catheter may produce artificial extra sounds by contact with the wall of the heart

More recently a range gated pulsed Doppler flowmeter has been developed that measures the average velocity of flow within a small sample volume at any point along the ultrasonic beam [5] In 1973 Johnson and associates [6] applied this Doppler echocardiography to the localization of a wide variety of cardiac murmurs comparing with the findings described by intracardiac phonocardiography in atrial septal defect the flow signal recorded with the Doppler in the tricuspid valve orifice and right ventricular inflow has increased intensity and turbulence during diastolic filling

In spite of their comment that there is a remarkable similarity between the Doppler findings and those obtained by intracardiac phonocardiography the turbulence due to shunt flow at the defect area was not yet described in their document probably because of technical difficulties in obtaining the Doppler signal of the septal area. For the time being intracardiac phonocardiography though invasive is considered to be the most useful method of performing the analysis of shunt murmurs across atrial septal defects

Summary

In order to study flow murmurs through atrial septal defects right heart catheterization was performed on 48 patients of secundum type four of primum type and five of probe patent foramen ovale with the double lumen phonocatheter of Lewis at the tip of which barium titanate was mounted

The flow murmurs at the defect area were classified into three patterns v murmur atriosystolic murmur and mid diastolic murmur

V murmur was continuous extending from late systole to diastole of low to medium pitch closely related to atrial v wave and augmenting with expiration It had no significant correlation to the ratio of left to right shunt It was recorded in 32 out of 48 cases of secundum type and one of primum type but not observed in probe patent foramen ovale

Atriosystolic murmur was noted in 17 of 48 cases of secundum type and one of primum type It was connected with atrial a wave

Mid diastolic murmur was found at the defect area in four subjects of secundum type It was thought to be an independent entity from v murmur and to be another one due to shunt flow through the septal defect since it had no relation to v wave but it was localized between v and a waves in the pressure curve of the right atrium It is different in localization from mid diastolic murmur due to relative tricuspid stenosis at the inflow tract of right ventricle

We thank Mr Kenji Mazaki for his technical assistance

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Feruglio[9], Effert[10] and Rautenburg[11] and their colleagues did not describe the flow murmurs, whereas Luisada[5], Liu[6], Lewis[7] and Köhler[12] and their co workers documented the evidence of diastolic murmur ascribed to left to right shunt at the atrial level

Somerville and Resnekov[13] showed that an immediate diastolic murmur in atrioventricular defects arose at the site of the atrial septal defect Wennevold[15] recognized an early diastolic murmur in atrial septal defect of secundum type, which was probably due to the shunt through the defect

Osher[16] indicated in the right atrium a continuous murmur extending from mid systole to diastole intensifying with expiration, but diminishing or disappearing with inspiration This right atrial murmur was not constant and was also confined to diastole

In 1969 Sakamoto and associates[14] designated the continuous murmur as v murmur, which originated at the defect area of atrial septal defect of secundum type because of close relation to atrial v wave They postulated that v murmur was essentially continuous, extending from systole to diastole crescendo decrescendo in configuration Plass and associates[17] also said that murmurs of low amplitude with presystolic, telesystolic and protodiastolic peaks were found in the right atrium of atrial septal defect

As far as v murmur is concerned, there is no disagreement between the findings obtained by Sakamoto and associates[14] and our data In our experience, an early diastolic murmur was also recorded in the right atrium during exploration for the detection of v murmur in the same patients who showed continuous murmurs at the different sites of the right atrium This early diastolic bruit is thought not to be an independent entity from v murmur, but to be an incomplete form of the latter because of parallel alteration to atrial v wave

In view of the study by Levin and associates[18] on atrial pressure flow dynamics in atrial septal defects, and the findings reported by Sakamoto and associates[14] it is likely that v murmur is produced by the pressure gradient between left and right atria A low pressure transducer should be used for correct measurement of atrial pressure

Weldon and associates[19] performed simultaneous recording of pressure and flow in dogs with experimental atrial septal defect, indicating that the flow pattern across the defect was not similar to the difference of both atrial pressures Herein there is a difficulty of relationship between flow and pressure

More recently, a noninvasive technique has been developed for assessing shunt volume with directional Doppler ultrasound which Kalmanson and associates[8,22] applied to the phasic analysis of left to right shunt in atrial septal defect measuring the alteration of flow velocity Furthermore, their data revealed that left to right shunt in atrial septal defect occurred from late systole to diastole with three flow patterns, in which S wave was localized at late systole to early diastole, D at mid diastole, and A at atrial contraction These three flow waves were found to be inclined to alter with heart rate and respiration Furthermore, there was a tendency to fusion of S and D waves on tachycardia

The research work performed by Gamble and associates[23] also revealed the evidence of three flow waves in atrial septal defect by means of fiberoptics for intracardiac oximetry in heart catheterization in contrast to two flow patterns propounded by Levin and associates[18] Commenting on this contradiction Kalmanson and associates[22] reported that either could occur

During exploration with the phonocatheter at the defect area a mid diastolic murmur was encountered in our study It is likely that the mid diastolic murmur is another one caused by shunt flow across the atrial septal defect since it has no relation to v wave, despite a slight change in vibratory events due to the effect of respiration and the positional shift of the transducer

Analogous to the possibility of fusion of S and D waves described by Kalmanson and associates[22] in their Doppler method, it is possible that v and mid diastolic murmurs become confluent on tachycardia during heart catheterization

With regard to the influence of respiration on flow velocity patterns S and D waves augmented on inspiration, according to Kalmanson and associates[22] In fact, Ross and associates[24] described an increase in the continuous murmur on inspiration in patients with left atrial hypertension and small atrial septal defect On the contrary, Osher,[16] Sakamoto and associates[14] and we revealed an increase in v murmur on expiration

In order to solve this discrepancy, it is of paramount importance to make a simultaneous

Changes in transthoracic electrical impedance during submaximal treadmill exercise in patients with ischemic heart disease— A preliminary report

V Balasubramanian MD FICA FCCP
R S Hoon MB FRCP FCCP FICA FAMS FACC
New Delhi India

Patients with angina pectoris have been demonstrated to develop significant alterations in left ventricular function and lung mechanics during exercise or pacing induced stress[1-3] These hemodynamic alterations have generally been investigated by invasive techniques and therefore remain confined to the research laboratory Noninvasive methods like apexcardiography phonocardiography systolic time intervals and isotopic perfusion scanning techniques are being increasingly used for investigating the functional alterations in angina pectoris[12-15] All these methods, however cannot give continuous on line data during exercise and electrocardiographic (ECG) monitoring still remains the most practical and widely used method of stress testing[illegible]

The theory technique and reliability of changes in mean transthoracic electrical impedance (TEI) to detect shifts in thoracic fluid volume have been reported by a number of workers[17-19] A controlled study of their efficacy in detection of thoracic fluid volume shifts in subjects exposed to high altitude hypoxia yielded impressive results[20] As this technique has been demonstrated to be an useful index of changes in pulmonary extravascular water space and left ventricular failure is a common accompaniment of the anginal syndrome it was hypothesized that TEI should show significant changes during exercise in patients with ischemic heart disease (IHD)[2, 20] The present study was therefore designed to investigate the changes in TEI in patients with IHD during submaximal treadmill exercise Findings of this entirely noninvasive study are reported

Material and methods

Thirty two male subjects with confirmed IHD (age range 40 to 57 years) were studied Fifteen subjects had classical anginal pain on exertion and others showed diagnostic ST depression without symptoms on stress testing None of the subjects had evidence of old myocardial infarction valvular disease or cardiac failure Twenty normal subjects in whom IHD had been excluded by detailed history physical examination, and maximal stress testing formed the control group (age range 21 to 47 years) Six subjects with pre excitation syndrome showing false positive ST segment changes on exercise formed the third group

All were subjected to submaximal exercises on a motor-driven treadmill* until the heart rate reached 85 per cent of predicted maximal for the age or until typical anginal pain or extreme fatigue supervened[16, 21] The exercise protocol used is shown in Table I

A bipolar ECG with the reference electrode at the manubrium sternum and the exploring electrode at the V_5 position was monitored continuously on a stress test monitor† and the graph recorded every minute An on line digital computer simultaneously displayed the heart

From the Unit of Chief Consultant (Medicine) *Army Hospital, Delhi Cantt, New Delhi, India*

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Reprint requests to M j V Balasubramanian, DC s Research Pool Officer Army Hospital, Delhi Cantt, New Delhi—110010 India

*Model E-10, manufactured by M/S Avionics, Ltd., Los Angeles, Calif.

†Mod 1 2500 manufactured by Avionics Research Products, Los Angeles, Calif

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Table II The TEI values observed during submaximal treadmill test in normal control subjects

Observation		Mean TEI (Ohms)	S E of mean	Mean % of HV	S E of mean	P*
Standing		26 6	0 6	97 5	0 6	NS
Hyperventilation (HV)		27 2	0 6	100	–	–
Exercise						
Stage	I	26 6	0 6	98 2	0 4	NS
	II	26 [illegible]	0 6	97.9	0.8	NS
	III	26 7	0 6	97.8	0 7	NS
	IV	26 7	0 6	97.9	0 7	NS
	V	26 7	0 7	99 1	0 4	NS
	VI	26 6	0 8	99.3	0 6	NS
Recovery						
Minute	1	27.3	0 6	100 8	0 6	NS
	2	27.2	0 6	100 0	0 6	NS
	3	27 1	0 6	100 0	0 6	NS
	4	27 1	0 6	100 0	0 6	NS
	5	27 1	0 6	100 0	0 6	NS

P p alu compared t HV l vels

Table III TEI values of patients with IHD during and after submaximal exercise

Stage	TEI (Ohms)		Per cent of control		ST segment	Mean heart rate	PN	PS†	Correlation‡
Resting	27 0	(0 4)§	97 1	(0 05)§	+0 05	76 0	NS	–	–
HV	27.8	(0 4)	100		–	81 6	NS	–	–
I	26.2	(0 5)	94 4	(0 7)	–0 53	104.2	< 0 001	< 0 001	NS
II	25 7	(0 5)	92 1	(1 0)	–1 01	112 7	< 0 001	< 0 001	< 0 01
III	25 2	(0 5)	90 0	(0 9)	–1 17	114 8	< 0 001	< 0 001	< 0 01
IV	24 4	(0 6)	87.2	(1.0)	–1 48	123 6	< 0 001	< 0 001	< 0 01
V	23 9	(0 4)	85 2	(1.3)	–1 93	125 7	< 0 001	< 0 001	< 0 01
VI	23 9	(0 7)	84 9	(1 8)	–2 22	134 6	< 0 001	< 0 001	< 0 05
Recovery									
1	24 3	(0 9)	90 4	(1 7)			< 0 001	< 0 001	–
2	26 1	(0 4)	94 2	(0 9)			< 0 001	< 0 001	–
3	27 0	(0 3)	97 3	(0 [illegible])			NS	NS	–
4	27.2	(0 4)	97 0	(0 5)			NS	NS	–
5	27 3	(0 4)	98 4	(0 3)			NS	NS	–

PN P valu compared to normal control s bjects
†PS P al compared to ontrol levels of the subject
‡C rrelation w th ST segment d pression
§Figures in parentheses indicate st dard rro of me n

increase from control values as the exercise progresses and reaches normal levels immediately on recovery The heart rate and ST segment responses are shown in Fig 3

Ischemic heart disease A total of 32 patients with confirmed IHD were studied Fifteen subjects developed anginal pain during the stress test and the other 17 did not have pain but showed horizontal ST segment depression of 1 0 mm or more during exercise The resting and post HV values of TEI were 27 0 (S E 0 4) and 27.8 (S E 0 4) ohms respectively These did not differ statistically from the control values During exercise the TEI dropped steadily from 100 per cent at HV to 94 4 92 1 90 0 87 2 85 2 and 84 9 per cent from Stages I to VI respectively All these values were highly significant ($p < 0.001$) when compared to the normal controls as well as the

Table I Treadmill protocol

Stage	Speed (KM/hr)	Angle (degrees)	Minutes
I	3 0	0	2
I	5 0	0	1
II	5 0	4	3
III	5 0	8	3
IV	5 0	12	3
V	5 0	16	3
VI	5 0	20	3
VII	7 0	20	3
VIII	9 0	20	3

rate, ST segment changes as computed against the PR segment in multiples of 0 1 mm, and warning of ectopics The subjects were instructed to follow standard instructions and the tests were conducted in a room kept at 28 ± 2° C with necessary safety precautions

The instrument used to measure the TEI in the present study comprised a circuit consisting of a 20 KHz oscillator which is coupled through a transformer to a modified Kelvin type bridge The current applied across the thorax was kept constant with a magnitude of 200μA The impedance was measured by balancing the bridge and observing the balance on an electronic detector through an amplifier A tetrapolar circular electrode system was employed with band electrodes, 1 cm wide made of copper mesh The electrode systems were placed in reference to constant anatomical landmarks The upper pair was located just above and below the cricoid cartilage and the lower ones at the level of the xiphisternum and 5 cm below it The current was passed between the two distal electrodes and the voltages were picked up in reference to the inner electrodes

The impedance circuit could be isolated from the subject by a cut off switch to eliminate disturbances in the ECG

The mean TEI was measured in sitting and standing postures, after maximal hyperventilation of 15 seconds, at the end of each stage of exercise and every minute during recovery until it reached the initial levels The ECG monitoring and TEI estimations were carried out by independant observers neither of whom was aware of the other s results

The data were analyzed by an ICL 1909 computer and statistical significance was calculated by Student s t test

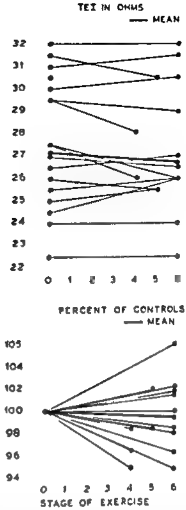

Fig 1 The first panel shows the observed TEI values in ohms at rest and at cessation of submaximal exercise in 20 normal control subjects The basal values range from 22 5 to 32 0 ohms (mean 27 2 ohms) On completion of submaximal exercise the TEI is either the same as the basal level slightly higher or lower The mean value has come down by 0 6 ohms only The second panel shows the changes as percentage of control values Here the mean TEI has come down by 0 7 per cent only

Results

Normal control subjects The mean TEI of the normal subjects ranged from 22 0 to 31 5 ohms in the sitting posture (mean 26 6 ohms S E 0 6) Standing did not produce any significant change in the values On hyperventilation (HV) for 15 seconds, the mean TEI ranged from 22 5 to 32 0 ohms (mean 27 2, S E 0 6) The value of each subject at the end of HV was taken as control and the subsequent values were expressed as percentage of control value The results are shown in Table II and depicted in Fig 1 It will be seen that the TEI shows an insignificant fall or a moderate

tests due to false ST changes Even though the ST segment became abnormal in the course of exercise the TEI remained within normal limits The heart rate ST segment and TEI response of these subjects along with the normal controls and IHD group are shown in Fig 3 The heart rate response and ST segment changes were more or less identical to the IHD group but the TEI changes were similar to the normal controls This may be of value in differentiating false positive exercise tests from true ST segment changes

Discussion

The clinical syndrome of angina pectoris is characterized by a constricting retrosternal pain tightness choking sensation or dyspnea These symptoms have been attributed to alterations in left ventricular function and the resulting changes in the pulmonary vasculature[8] Muller and Ronvik[20] observed At the height of a spontaneous attack of anginal pain transitory gross signs of left ventricular failure were seen with increased pulmonary capillary pressure up to levels where pulmonary edema may develop Increased left ventricular filling pressure has been reported to be a consistent accompaniment of angina pectoris generally preceding the appearance of chest pain It has also been reported that an abnormal exercise ECG test provided a reliable clue to an associated abnormal increase in left ventricular filling pressure during exercise Martin and McConahay[7] observed that pulmonary artery wedge pressure during exercise increased significantly along with ST depression

These hemodynamic alterations in turn lead to an increased thoracic blood volume and then to an increase of pulmonary extravascular water space[2] If a reliable technique is available to measure these alterations noninvasively it would offer a significant advance in the field of stress testing as it would measure an accepted hemodynamic alteration Transthoracic electrical impedance measurements seemed to be a suitable technique as estimations of changes in thoracic blood volume is possible by this noninvasive technique

Luepker Michael and Warbasse[7] found that in pulmonary edema induced in experimental animals the changes in TEI preceded and later correlated well with increase in central blood volume and pulmonary extravascular volume

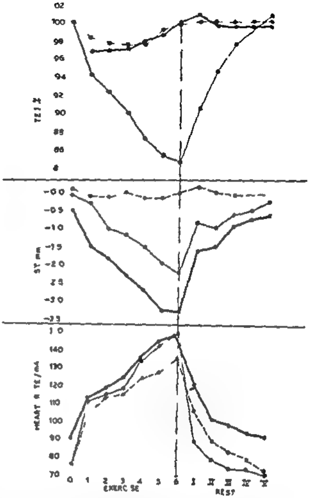

Fig 3 The mean values of ST segment depression heart rate and TEI values are shown for each stage of exercise and during recovery In normal subjects (dashed lines) the TEI and ST segment are unaffected In patients with IHD (thin straight lines) there is a corresponding decrease of TEI with ST depression and the recovery is slow In subjects with false ST depression (heavy lines) the ST shows a steep fall but the TEI remains unchanged The heart rate response is essentially equal in all groups

determined by double indicator dilution technique Van de Water[3] [4] and Pomerantz and their colleagues[3] [10] and other authors[12] [7] have reported the use of TEI in clinical work Roy and co workers found the technique to be valuable in detection of high altitude pulmonary edema The technique suitably modified with a tetrapolar circular lead system is not unduly affected by respiration but has a linear correlation with pulmonary blood volume[17] [11] The current study was therefore planned to discover the effect of submaximal treadmill exercise on the mean TEI and designed to be a totally noninvasive one

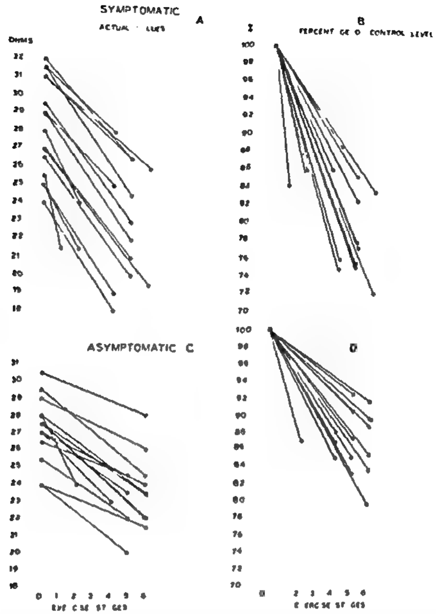

Fig 2 This shows the TEI changes of subjects with IHD Panels *A* and *B* show the values of 15 subjects who developed anginal pain during the test The basal values vary from 24 to 32 ohms and at the onset of anginal pain a drop of 11 to 28 per cent of the control is observed Panels *C* and *D* show the changes in subjects who had ST depression alone without pain and the drop in TEI ranges from 7 5 to 20 per cent As compared to the normal control subjects where there was a drop of only 0 7 per cent of mean TEI patients with IHD show a drop of 15 1 per cent of the mean value

subjects' own control levels obtained during HV The TEI in ohms with the percentage values are shown in Table III and Figure 2

During recovery from exercise the TEI did not normalize immediately It took more than 3 minutes in most of the subjects to reach control values The values obtained on the first and second minute of recovery period were significantly different ($P < 0\,001$) from the normal controls as well as the subjects' control levels

The extent of ST depression as obtained from the digital readouts from the monitor was then correlated to the severity of TEI changes with Spearman s rank order correlation test The first stage exercise values were not significant but the TEI II to VI stage observations showed a significant correlation ($P < 0\,01$, VI stage $P < 0\,05$)

The maximum TEI change observed in the subjects who developed anginal pain during the test was compared with those showing asymptomatic ST depression The results are shown in Fig 2 It was clearly seen that the change was steeper and more profound in the symptomatic subjects as compared to the asymptomatic group ($P < 0\,001$)

False ST segment depression Six cases of pre excitation syndrome with no evidence of IHD were studied All of them had abnormal stress

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In normal control subjects, the TEI varies from 22 0 to 31 5 ohms, the mean being 26 6 ohms The TEI of a subject varies with the height, weight, chest measurements, and body build Due to the wide variations in the control value the changes in TEI are conventionally expressed as percentage of the basal levels [23] As the technique measures changes in thoracic blood volume rather than absolute values it is ideally suited for comparative studies where the base line impedance is available As increase in minute ventilation is a physiological accompaniment of severe exercise controlled HV was taken as the baseline in this study Normally increased ventilation during exercise tends to augment TEI values on the one hand and increased thoracic blood volume tends to decrease the TEI on the other [23] As we did not find a significant change in TEI during exercise it is reasonable to conclude that these changes neutralize each other in normal subjects

The profound hemodynamic changes resulting from angina, however, produce a marked drop in the TEI overshadowing the physiological rise due to HV The TEI gradually decreases as the exercise progresses reaching the peak at the onset of pain or at maximal ST depression During recovery the TEI does not return to normal immediately but takes 3 to 5 minutes to reach control levels In subjects with anginal pain developing during the test the TEI changes are more profound, indicating the severity of the hemodynamic changes In asymptomatic ST depression also there is a significant change from normal but less when compared to the subjects with anginal pain Further there seems to be a significant correlation between the extent of ST depression and TEI changes This offers possibilities for long term follow up of these cases and offers a method to objectively evaluate efficacy of antianginal drug therapy

The findings in our small series of six subjects with false ST depression indicate that TEI may be valuable in differentiating such changes from true ischemic heart disease The TEI remained normal throughout the exercise protocol despite a rapid fall in the ST segment and increase in heart rate as these are not accompanied by any significant hemodynamic alterations

Estimation of mean TEI during exercise offers a significant advance in the field of stress testing for objective and total evaluation of coronary artery disease The technique is totally atraumatic, easy to perform, and does not interfere with ECG monitoring The equipment is inexpensive and is available with digital readouts enabling instantaneous data collection during the test As it measures a known quantifiable pathophysiological alteration in anginal syndrome it may have diagnostic therapeutic and prognostic implications It is recommended as a valuable screening procedure in addition to electrocardiography

Our study was planned to be an entirely noninvasive one and is preliminary and clinical It is essential to correlate the changes in TEI to hemodynamic changes during atrial pacing exercise and the extent of disease by coronary angiography in patients with ischemic heart disease Once such a correlation is established the procedure will have a wider and universal application

Summary

Twenty normal subjects and 32 patients with ischemic heart disease (IHD) were subjected to submaximal treadmill exercise The mean transthoracic electrical impedance (TEI) was measured with a tetrapolar lead system and the changes were correlated to the extent of ST depression observed on an on line digital computer Six subjects of pre excitation syndrome with false ST depression were also studied The normal subjects did not show a significant change of TEI during exercise The patients with IHD showed a steady and significant decrease in TEI, correlating with the extent of ST depression Recovery was slow after the cessation of exercise The subjects with false ST changes showed no decrease of TEI The changes were more profound in subjects who developed anginal pain during the test These findings are attributed to an increase in the thoracic blood volume and pulmonary extravascular water due to transient left ventricular dysfunction in angina

The instrument used in this study was designed and fabricated by Prof S K Guha and his colleagues of the Biomedical Engineering of IIT New Delhi India The technical help of Mr M R Khan of the same department and secretarial assistance by Hav/Clk K L Yadav of Army Hospital Delhi Cantt India is acknowledged We are grateful to the Director General Armed Forces Medical Services India for permission to publish the paper

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Table I Summary of clinical data

Case No	*Age (yr)/sex*	*Diagnosis*	*RV syst pr (mm. Hg)*	*LVFDV (ml.)*	*LV wall thickness at end diastole (mm.)*	*LV mass (Gm.)*	*Relative LV wall thickness at end diastole*
Controls							
1	39/F	OTAP	31	87	7.5	101	0.2b
	24/F	OTAP	19	93	6.3	103	0 22
3	30/F	Mild MS with mild AI	38	107	8 0	121	0.24
4	21/M	Mild MSI with trivial AI	35	98	6 0	83	0.20
5	26/F	OTAP	39	97	6.5	88	0.22
[illegible]	19/F	Mild PSI	30	84	9 4	132	0.30
7	19/F	Trivial VSD	26	76	6 3	75	0.22
8	16/F	OTAI	30	96	7 9	111	0.24
9	35/F	OTAP	29	102	9 0	137	0.28
10	45/M	Trivial VSD	29	103	8 9	135	0.26
11	33/M	Mild MS	38	148	7 6	148	0.20
1?	16/F	Mild PS	32	121	6.2	134	0.24
Patients with eccentric LVH							
13	18/F	PDA with moderate shunt	19	219	7 1	150	0 18
14	15/M	PDA with moderate shunt	28	236	8.5	212	0.20
1?	24/F	PDA with moderate shunt	34	273	8.8	237	0 20
[illegible]	16/M	PDA with large shunt	5?	3?6	9 0	291	0 18
17	16/M	PDA with large shunt	6?	4?9	9 0	316	0 18
[illegible]	21/M	VSD with moderate shunt	24	2?9	7 9	201	0 18
19	??/M	VSD with AI	27	19?	9.3	207	0.22
20	21/M	Moderate or severe AI	?7	356	7 2	217	0 16
21	40/M	Severe AI	?6	514	8 7	339	0 16
22	25/M	Moderate AI with mild AS	38	?49	10 1	334	0.22
23	3?/M	Severe AI	30	506	11 7	479	0.22
?4	32/M	Severe AI	55	630	12 0	566	0.22
25	19/M	VSD with small shunt	3.	212	7.9	1 9	0.20
26	21/M	VSD with moderate shunt	28	150	7.9	150	0.22
27	28/F	Moderate MI	3?	372	6.3	201	[illegible] 14
28	29/M	VSD with moderate shunt	?9	203	7 6	167	0.20
29	23/M	VSD with severe AI	28	700	8 5	388	0 14
30	26/F	Severe MI with moderate AI	50	388	5 8	181	0 12
31	47/M	Mild ASI mild MSI	40	213	6 7	150	0 18
32	?6/F	Moderate MSI ASI	46	271	8.5	225	0.20
[illegible]	?9/M	Moderate MI	26	235	8 6	206	0.20

OTAP Occlusive thr mboaortopathy MS m tral st nosis AI a rtic insuffic ncy PSI pulmonic stenoinsufficiency VSD ventricular septal defect PS pulmonic tenosis, PDA, patent d ctus arteriosus AS aortic stenosis MI mit al insufficiency ASI a rt c stenoinsufficiency MSI mitral stenoinsufficiency

trophy pattern[1] in the vectorcardiogram were excluded from the control group In general we consider that in patients with either almost normal or definite left ventricular hypertrophy pattern of the VCG the electrical forces depending on the right ventricular free wall are relatively small the reason being that the weight of right ventricular free wall is merely one fourth of the total weight of left ventricular free wall and the septum in normal subjects In all cases a routine cardiac catheterization and angiocardiography were done Angiocardiography was performed with power injection of contrast material into either the right or left cardiac chamber at a maximal rate of six films per second using a Schonander biplane film changer In angiocardiography LVEDV LV wall thickness (h) in end diastole LV mass and relative wall thickness in end-diastole (2h/D+2h) defined by us on A P films were measured where D was calculated on A P films as 4A/πL and A was the planimetered area of the LV image on A P films LVEDV was calculated from the angiocardiogram on A P film according to the formula by the area length

High reliability rates of spatial pattern analysis by vectorcardiogram in assessing the severity of eccentric left ventricular hypertrophy

Kazutoshi Ishizawa, M D
Kyoko Ishizawa, M D
Masakazu Motomura, M D
Tomotsugu Konishi M D
Akira Wakabayashi, M D
Kaichiro Ishikawa, M D
Yoshitsugu Nohara, M D
Chuichi Kawai M D
Hisaaki Koie M D
Kyoto and Tenri Japan

Excellent studies[1-5] of anatomic and electrocardiographic (ECG) correlation of left ventricular hypertrophy (LVH) have been documented yet none has demonstrated a close relationship between any specific ECG abnormality and the ventricular weight as determined by the autopsied material or the angiocardiogram Recently, it was reported that a highly significant correlation was obtained between the angiocardiographic left ventricular mass (LV mass) and the magnitude of the maximal QRS vector in the horizontal plane[6] or that of the spatial maximal QRS vector[7] in living patients with the Frank system

The present study was undertaken to explore indices of the vectorcardiogram (VCG) which could be most reliable for assessing the severity of eccentric LVH by correlations between the LV mass determined by angiocardiogram and 26 VCG measurements including QRS and T loops In this paper eccentric LVH is defined as LV chamber enlargement with normal or slightly increased wall thickness[8]

From the Third Department of Medicine Faculty of Medicine Kyoto University Kyoto and Department of Cardiovascular Surgery Tenri Hospital Tenri Japan

A summary of this study was presented at the thirty ninth Annual Meeting of the Japanese Circulation Society held in Kyoto March 31 April [redacted] 1975

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Reprint requests Kazutoshi Ishizawa M D Third Department of Medicine Faculty of Medicine Kyoto University Shogoin Sakyo ku Kyoto 606 Japan

Patients and methods

Subjects included 33 patients with various heart diseases, including 12 control subjects with the normal LV cavity and wall thickness and 21 with eccentric LVH (Table I) LV mass or the corrected LV mass for BSA and VCG measurements were correlated for all subjects (Table II) Patients with 150 ml or greater of left ventricular end diastolic volume (LVEDV) and 150 Gm or greater of LV mass were grouped as those with eccentric LVH In this eccentric LVH group the LV wall was normal or slightly thickened, while the relative wall thickness was nearly normal or decreased, and the LVH pattern only was observed according to the criteria[10] Patients with incomplete left bundle branch block[12] were not included in the LVH group Although some of the patients in the control group presented disorders which could lead to left ventricular enlargement (aortic insufficiency, mitral insufficiency) significant LVH was not demonstrated angiographically, because of slight regurgitation In two patients with ventricular septal defect left to right shunt was not detectable by the Fick method and the LV mass was normal Those with increased right ventricular systolic pressure (40 mm Hg or over) or a right ventricular hyper-

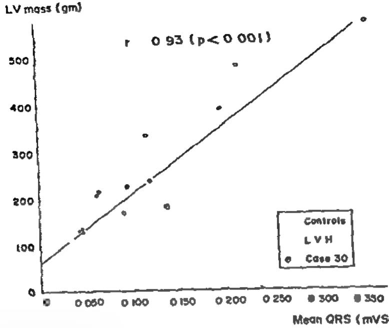

Fig 1 Relationship between the magnitude of the spatial mean QRS and LV mass in all 33 cases ($r = 0.93$) This finding strongly suggests that increased QRS voltage and usual prolonged QRS duration in eccentric LVH are due to an increase in LV mass

zontal left was 0° horizontal right was +180° anterior was +90° and posterior was −90°

Microscopic analysis was done on only one patient (case 30) with markedly discordant T loop in VCG The anterior papillary muscle of the left ventricle was obtained at the time of surgery for mitral valve replacement From the biopsied specimens transverse diameters of cardiac muscle cells the grade of myocardial fibrosis and various degenerative findings were examined under light microscopy

Results

Table I indicates the age sex clinical diagnosis right ventricular peak systolic pressure (RV syst pr) LVEDV LV wall thickness at end diastole LV mass and relative LV wall thickness at end diastole of the total 33 cases Table II demonstrates the linear correlation coefficients and p values which were obtained by correlations between the VCG variables and the LV mass or the corrected LV mass of BSA As shown in Table II regarding the QRS loop the most significant correlations were obtained between the LV mass and the magnitude of the spatial mean QRS vector and the time of the spatial maximal QRS vector of which values were 0 93 and 0 93 respectively ($p < 0.001$) as shown in Figs 1 and 2 These highly significant correlations suggest that the VCG analysis is not only useful but reliable in assessing the severity of eccentric LVH Concerning the T loop the most significant correlations were obtained between the LV mass and the spatial QRS-T angle the spatial mean QRS T angle and mean QRS/G of which r values were 0 75 0 76 and 0 76 respectively ($p < 0.001$) Here G was a ventricular gradient vector Thus the correlation between the LV mass and T loop was less in comparison with that regarding the QRS loop From these findings it is suggested that T loop change observed in eccentric LVH may be related not only to increased LV mass but to other factors such as myocardial ischemia or other origins

Other findings in this study are worthy of comment Fig 3 demonstrates the relationship between the LV mass and the spatial mean QRS T angle Although in case 30 the magnitude of the spatial mean QRS vector and the time of the spatial maximal QRS vector increased proportionally to a LV mass (Figs 1 and 2) the spatial mean QRS T angle widened much more than that expected with an increase in LV mass (Fig 3) Angiocardiogram revealed a moderate LV

Table II. Correlation coefficients and p values for 33 patients

	LV mass	LV mass/M²
I. Instantaneous QRS and T vectors		
Max. QRS vector		
Mag.*	0.84 ($p < 0.001$)	0.86 ($p < 0.001$)
Az.	−0.51 ($p < 0.01$)	−0.51 ($p < 0.01$)
Ele.	0.47 ($p < 0.01$)	0.47 ($p < 0.01$)
Time	0.93 ($p < 0.001$)	0.92 ($p < 0.001$)
Max. T vector		
Mag.	0.51 ($p < 0.01$)	0.50 ($p < 0.01$)
Az.	0.65 ($p < 0.001$)	0.63 ($p < 0.001$)
Ele.	0.75 ($p < 0.001$)	0.76 ($p < 0.001$)
Q vector		
Mag.	0.66 ($p < 0.001$)	0.70 ($p < 0.001$)
Az.	−0.01 ($p > 0.1$)	−0.01 ($p > 0.1$)
Ele.	−0.27 ($p > 0.1$)	−0.24 ($p > 0.1$)
Time	0.66 ($p < 0.001$)	0.63 ($p < 0.001$)
QRS-T angle	0.75 ($p < 0.001$)	0.75 ($p < 0.001$)
QRS/T	0.50 ($p < 0.01$)	0.54 ($p < 0.01$)
QRS duration	0.70 ($p < 0.001$)	0.68 ($p < 0.001$)
II. Mean QRS, mean T, and ventricular gradient vectors		
Mean QRS vector		
Mag.	0.91 ($p < 0.001$)	0.92 ($p < 0.001$)
Az.	−0.57 ($p < 0.001$)	−0.57 ($p < 0.001$)
Ele.	0.63 ($p < 0.001$)	0.62 ($p < 0.001$)
Mean T vector		
Mag.	0.54 ($p < 0.01$)	0.49 ($p < 0.01$)
Az.	0.67 ($p < 0.001$)	0.69 ($p < 0.001$)
Ele.	0.64 ($p < 0.001$)	0.65 ($p < 0.001$)
G		
Mag.	0.32 ($p < 0.1$)	0.29 ($p > 0.1$)
Az.	−0.73 ($p < 0.001$)	−0.75 ($p < 0.001$)
Ele.	0.52 ($p < 0.01$)	0.49 ($p < 0.01$)
QRS-T angle	0.76 ($p < 0.001$)	0.76 ($p < 0.001$)
QRS/G	0.76 ($p < 0.001$)	0.78 ($p < 0.001$)
QRS/T	0.50 ($p < 0.01$)	0.54 ($p < 0.01$)

Max. = Maximal; mag. = magnitude (mV or mV-sec); az. = azimuth; ele. = elevation; G = ventricular gradient vector. All instantaneous and mean vectors were used as a spatial sense.

method of Sandler and Dodge.[11] LVEDV = 0.951 × (4/3)π × (D/2) × (L/2) − 3.0.

LV mass was calculated as follows: LV mass = (total LV volume − LVEDV) × 1.050, where total LV volume was calculated as the volume of the left ventricular myocardium plus chamber at end diastole. Total LV volume = 0.951 × (4/3)π × [(D/2) + (h)] × [(L/2) + (h)] − 3.0.

LV wall thickness (h) in end diastole was measured on the A-P films at the lateral free wall along the line of the equator. All measurements from A-P films were corrected for nonparallel x-ray beam distortion by the correction factor determined for the A-P plane during biplane filming.

A vectorcardiogram utilizing the Frank system and its scalar leads was taken during the hospitalization not more than 1 week prior to the catheterization and angiocardiography. Vectorcardiographic loops were produced on a vectorcardiograph equipped with cathode ray oscilloscopes (Fukuda Electro VA-3C5) and photographed on 35 mm. film. Scalar ECG's were recorded on a direct writing recorder (Fukuda Electro 3CH) at a paper speed of 100 mm. per second. VCG measurements were calculated manually from the X, Y, and Z scalar leads. The magnitude of the spatial mean QRS vector was calculated from the X, Y, and Z components which were the algebraic addition of the positive and negative areas under the QRS complex in each lead.[8]

The spatial maximal QRS and Q vectors were analyzed by the method of Estes and associates.[15] The time of the spatial maximal QRS vector was used as "spatial VAT" and was estimated as the time from the beginning of the ventricular depolarization to the spatial "R" with the use of the simultaneously recorded X, Y, and Z scalar leads. Definition of the ventricular gradient vector (G) was a single vector as measured from the VCG, the mean difference in duration of the excited state.[16,17] Its value was calculated from the X, Y, and Z components that were obtained by the algebraic sum of QRS and T areas (positive or negative) in each lead.

Calculations of the spatial instantaneous and mean vectors were as follows: (1) The spatial magnitude (SM) according to the Pythagorean theorem:

$$SM = \sqrt{x^2 + y^2 + z^2}$$

(2) Azimuth (H°) according to the formula:

$$\tan H° = z/x$$

(3) Elevation (V°) according to the formula:

$$\cos V° = -y/\sqrt{x^2 + y^2 + z^2}$$

(4) QRS-T angle (θ°) according to the formula:

$$\cos \theta° = (QRSx \cdot Tx + QRSy \cdot Ty + QRSz \cdot Tz)/|QRS| \cdot |T|$$

For elevation, inferior vertical was 0°, superior vertical was +180°. Regarding azimuth, hori-

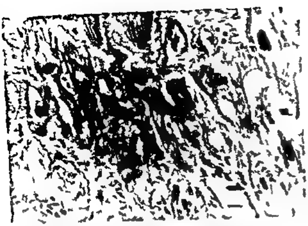

Fig 4 Light micrograph of the anterior papillary muscle of the left ventricle from Case 30 Moderate interstitial fibrosis and the degradation of the sarcoplasm in the perinuclear region are evident (Hematoxylin and eosin stain scale bar = 20 μ.)

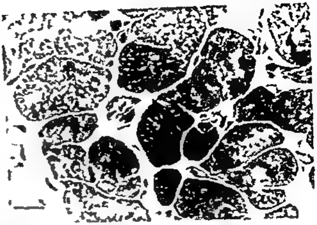

Fig 5 Light micrograph of semithin section (1 μ thick) of the anterior papillary muscle of the left ventricle from the same patient as in Fig 4 Muscle cells are hypertrophied with transverse diameters ranging from 12 to 48 μ (average 28 μ) In addition the abnormally dilated T system and the vacuolar degeneration are observed (Alkaline toluidine blue stain scale bar = 20 μ.)

chamber enlargement with LVEDV of 388 ml and markedly decreased relative wall thickness (0.12) of which the control value was 0.24 ± 0.03 (mean ± S.D.) This finding indicated inadequate hypertrophy[6] in case 30

In addition light microscopic findings of the LV obtained at operation showed markedly enlarged cardiac muscle cells with transverse diameters ranging from 12 to 48μ (average 28μ) moderate interstitial fibrosis abnormally dilated T system and degeneration such as residual body vacuolar degeneration metachromasic substance stained with alkaline toluidine blue in the sarcoplasm and degradation of the sarcoplasm in the perinuclear region (Figs 4 to 6) These observations give added support to the hypothesis that widening of the QRS-T angle does not always parallel an increase in LV mass and may be related to a certain functional and morphologic alterations in the cardiac muscle including metabolic disturbance[19] and mechanical burden [18]

Discussion

A highly significant correlation was obtained between the LV mass and the magnitude of the spatial mean QRS vector (r = 0.93 p < 0.001) This finding shows that increased QRS voltage and usual prolonged QRS duration in eccentric LVH are due to an increase in LV mass On the other hand the time of the spatial maximal QRS vector (spatial VAT) also correlated to the LV mass (r = 0.93 p < 0.001) This fact strongly suggests that delayed VAT in eccentric LVH is

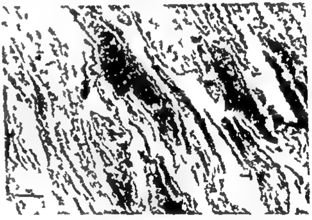

Fig 6 Light micrograph of semithin section of the anterior papillary muscle of the left ventricle from the same patient as in Figs. 5 and 6 Residual body and metachromasic substance stained with alkaline toluidine blue are noted (Alkaline toluidine blue stain scale bar = 20 μ.)

based completely on anatomic alteration namely the greater distance of the intraventricular conducting pathways caused by LV dilatation In addition this hypothesis is supported by our previous report[7] as VAT highly correlated to the length of the long axis of LV at end diastole However other explanations have been proposed regarding the prolonged VAT LV dilatation may produce a stretching of the conduction system which in turn reduces its cross sectional diameter thereby decreasing the powers of conductivity[2] Wilson and associates[21] stated that the right bundle branch block pattern in cases of acute cor pulmonale was due to a decreased density of the

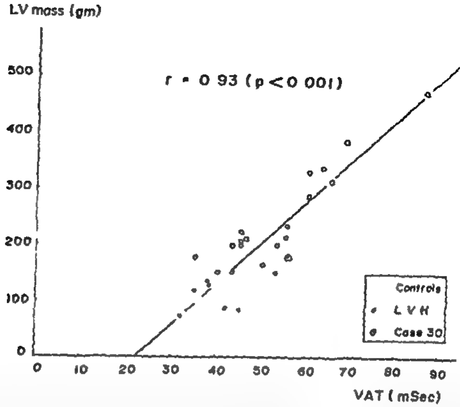

Fig 2 Relationship between the time of the spatial maximal QRS vector (VAT as a spatial sense) and LV mass (r = 0 93) This finding also strongly suggests that prolonged VAT observed in eccentric LVH closely relates to an anatomic alteration namely the greater distance of the intraventricular conducting pathways caused by LV dilatation because an increase in LV mass is usually paralleled by the grade of the chamber enlargement in this type of LVH

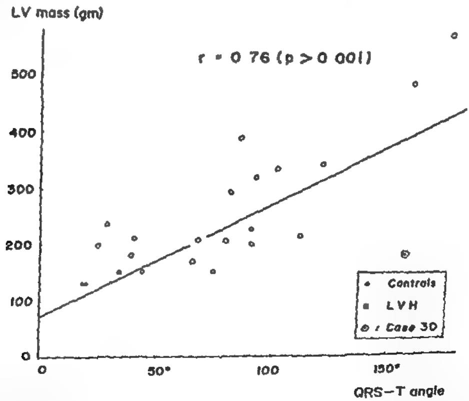

Fig 3 Relationship between the spatial mean QRS T angle and LV mass (r = 0 76) This correlation was significantly less than that regarding the QRS loop such as those shown in Figs 1 and 2 In case 30 the spatial mean QRS T angle widened much more than that expected with an increase in LV mass. Angiocardiogram of this patient revealed a moderate chamber enlargement with markedly decreased relative wall thickness Microscopic findings of the left ventricle obtained at operation showed the enlarged cardiac muscle cells moderate interstitial fibrosis abnormally dilated T system and various degenerations (Figs 4 5 and 6) Such findings suggest that the spatial mean QRS T angle relates to a certain altered cardiac muscle state in addition to an increase in LV mass

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junctions between Purkinje and ordinary muscle in certain areas, as a result of dilatation[9] Thus, both assumptions were based on functional data rather than anatomic considerations In the present study, LV mass per square meter of body surface area also correlated to all VCG measurements but the r values did not increase, they stayed the same

Summary

In 33 patients including 12 control subjects and 21 with eccentric LVH LV mass determined by angiocardiogram was correlated to 26 VCG measurements (Frank system) calculated from the scalar X Y, and Z leads The results demonstrated that the most reliable indices of VCG in assessing the severity of eccentric LVH determined by angiocardiogram were the magnitude of the spatial mean QRS vector and the time of the spatial maximal QRS vector (spatial VAT), of which correlation coefficients were 0 93 and 0 93 respectively Such high correlation coefficients have never been obtained with the usual ECG analysis These findings strongly suggest that (1) increased QRS voltage and usual prolonged QRS duration in eccentric LVH are due to an increase in LV mass and (2) prolonged VAT observed in eccentric LVH is closely related to an anatomic alteration namely the greater distance of intraventricular conducting pathways as the result of LV dilatation as an increase in LV mass is usually paralleled by the grade of the chamber enlargement in this type of LVH Regarding the T loop correlations between the LV mass and the VCG measurements were less as compared to those of the QRS loop In general T changes in moderate or severe LVH may be also related to a certain altered cardiac muscle state, in addition to an increase in LV mass Angiocardiographic and light microscopic findings of a patient with eccentric LVH in whom a widened QRS T angle was demonstrated to an extent much more than that expected with an increase in LV mass are presented and discussed The spatial pattern analysis by VCG is very useful and reliable in assessing the severity of eccentric LVH

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Assessment of antiarrhythmic efficacy The efficacy of mexiletine was assessed by one or more of the following (1) A continuous 24 hour electrocardiogram (ECG) was recorded on tape during initiation of therapy (2) Outpatients were seen at intervals of 1 to 6 weeks and a 5 minute ECG rhythm strip was always recorded with a full ECG if indicated Blood was taken at each visit for hematological and biochemical examination (3) Portable 24 hour ECG tape recorders were used in 20 outpatients (4) Seven patients were readmitted for ECG monitoring during withdrawal (and if necessary recommencement) of mexiletine (5) Strong circumstantial evidence is reported—for instance the sudden death of a patient previously well controlled on long term mexiletine a few days after this was stopped or reduced

ECG monitoring ECG tapes were assessed visually during replay at 60 × real speed with write out of abnormal sections on paper for detailed analysis In addition some tapes were analyzed with a hybrid analogue digital computer However the presence and nature of abnormal rhythms particularly in portable tape records were always confirmed by visual inspection of the original record Criteria for success of therapy involved absence of the ventricular arrhythmias defined above and freedom from toxicity Therapy was regarded as successful when the arrhythmias were abolished partial success was defined as a decrease in treatable VES by more than 75 per cent with abolition of VT Attention was also paid to the frequency of ventricular extrasystoles and the effect upon these of altering the dose of mexiletine though a simple increase in frequency was not automatically counted as a failure of therapy

The replay machine and portable tape recorders were manufactured by the Oxford Instrument Company Cassettes (C 120) were used once only the ECG being transferred via the Oxford replay machine at 60 × real speed to a 7 inch tape spool This was then replayed for analysis on a large variable speed tape deck Sticking of the C 120 cassette tapes during recording due to uneven spooling was largely avoided by the use of Memorex tapes exclusively though there were multiple technical problems with the tape recorders particularly initially

Hematological and biochemical investigations Full blood counts (including platelet white cell and differential count) and estimations of serum urea electrolytes bilirubin glutamic oxal acetic transaminase (SGOT) alkaline phosphatase antinuclear factor (ANF) and serum folate and B_{12} levels were performed at intervals of 1 to 6 weeks

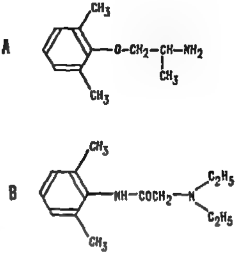

Fig 1 Structural formulas of (*A*) mexiletine and (*B*) lignocaine

Plasma concentrations of mexiletine Plasma concentrations of mexiletine were measured at frequent intervals in all patients and correlated with antiarrhythmic and toxic effects Mexiletine was estimated by gas liquid chromatography with a nitrogen sensitive flame ionization detector by a method developed in our laboratories[8]

Results

Antiarrhythmic activity The results of treatment with mexiletine are summarized in Tables I to IV Following the start of treatment no ventricular arrhythmias as previously defined were observed in 19 (79 per cent) of the patients Control in two of the latter was improved by the addition of practolol In four patients arrhythmias were successfully controlled but side effects necessitated reduction of the dose to less effective levels (see below)

One patient of 11 in the postmyocardial infarction group two of seven in the IHD group and one of six in the idiopathic ventricular arrhythmia group were classified as only partially successful and there was one failure in the IHD group (Table I) Five inpatients redeveloped VT and one multiple VES after stopping mexiletine

Long-term treatment of ventricular arrhythmias with oral mexiletine

R G Talbot, M R C P
D G Julian, M D
L F Prescott, M D
Edinburgh Scotland

Mexiletine (Ko 1173) is a new drug recently found to be effective in the treatment of ventricular arrhythmias[1-6] Structurally it resembles lignocaine (Fig 1), but is metabolized very slowly and can be given orally Previous work demonstrated its effectiveness when given either intravenously or orally[3,4] and it seemed to have a particular potential as a long term oral agent because of its long plasma half life (10 to 25 hours)[4,5]

In this paper we report the use of oral mexiletine in a series of 24 patients treated for periods ranging from 1 to 16 months, during which time regular observations were made concerning efficacy and possible toxicity

Patients and methods

Patients Twenty one male and three female patients were studied Their ages ranged from 32 to 73 years (mean, 53 years)

At the time therapy with mexiletine was commenced all suffered from one or more of the following ventricular arrhythmias (1) (a) occurring on the T wave (b) with a coupling interval less than 0 40 sec, (c) multiform, (2) ventricular tachycardia (VT), (3) ventricular fibrillation (VF)

The patients themselves fell into three main groups (A) acute myocardial infarction complicated by ventricular arrhythmias necessitating initial therapy with intravenous lignocaine (of the 11 patients in this group, six were arbitrarily treated with oral mexiletine instead of the customary course of oral procainamide, five had more persistent ventricular arrhythmias in the coronary care unit and mexiletine was substituted for less effective therapy, (B) ischemic heart disease (IHD) with recurrent ventricular arrhythmias in the absence of recent infarction seven patients, (C) idiopathic ventricular arrhythmias [six patients—four with recurrent VT and two with multiple ventricular extrasystoles (VES)]

Administration of mexiletine This was given in capsules containing either 200 or 50 mg The usual starting dose was 400 to 600 mg, followed 4 to 6 hours later by the commencement of maintenance therapy at a dose of 150 to 350 mg every 8 hours Previous studies have shown that these doses usually produce plasma concentrations within the therapeutic range of 0 75 to 1 5 μg/per milliliter with little risk of toxicity[3] The oral loading dose was omitted in patients who had previously been on intravenous mexiletine

Duration of therapy The duration of treatment depended on the initial diagnosis and the results of therapy Patients with arrhythmias following an acute myocardial infarction were treated for a minimum of one month and then observed after mexiletine was discontinued Patients with more persistent arrhythmias (such as Groups B and C) were treated for longer periods

Mexiletine was given over a total period of 11 4 patient years with individual periods of treatment ranging from 1 to 16 months (mean 24 weeks) The mean periods of therapy in each group were Group A (acute myocardial infarction) 3 7 months Group B (ischemic heart disease), 5 1 months, and Group C (idiopathic ventricular arrhythmias), 10 0 months

From the Departments of Cardiology and Therapeutics Royal Infirmary Edinburgh, Scotland

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Reprint requests [illegible] R [illegible] Talbot M R C P Department of Cardiology The Royal Infirmary Edinburgh EH3 9YW Scotland U K

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Table III Summary of oral mexiletine therapy Group B Ischemic heart disease

Initials	*Age*	*Sex*	*Weight (Kg)*	*Arrhythmia*	*Duration of therapy (mo)*	*Control*	*Comments*
J M	[illegible]	F	45	VES	6 7	Fair	Frail old woman Dizziness and tremor Limited dose Combination with practolol better
J C	73	F	5[illegible]	VT (recurrent)	5 0	Fair	Frail old woman Blurred vision Limited dose Loss of control as dose decreased Various antiarrhythmic combinations tried unsuccessfully Eventual myocardial infarction
F McA	53	M	88	VES VT (recurrent)	2 8	Good	
A A	64	F	79	VT (recurrent)	1 0	Poor	Frail old woman Blurred vision and nausea intolerant of small doses Stopped Sudden death 3 wk later
G S	70	M	61	VT (recurrent)	10 0	Good	VT recurred on day 3 after mexiletine electively withheld
J R	59	M	80	VES	3 8	Good	Readmitted with acute myocardial infarction and supraventricular tachycardia Mexiletine stopped VT 2 days later
G B	63	M	80	VES	8 0	Good	
Mean	63 4				5 1		

Table IV Summary of oral mexiletine therapy Group C Idiopathic ventricular arrhythmias

Initials	*Age*	*Sex*	*Weight (Kg)*	*Arrhythmia*	*Duration of therapy (mo)*	*Control*	*Comments*
W P	31	M	70	VT (recurrent)	15 0	Good	Mexiletine electively stopped after 1[illegible] mo Accelerated idioventricular rhythm palpitations tolerable but no VT
J B	41	M	100	VT (recurrent)	1[illegible] 0	Good	VT recurred on day 3 after mexiletine electively withheld
R S	62	M	9[illegible]	VES[illegible] VT	15 0	Good	Multiform VES on day 2 after mexiletine electively withheld
G K	31	M	6	VES	4 0	Fair	Dizziness Tolerated only moderate dose and control only fair at this level
J W	63	M	85	VT (recurrent)	[illegible] 8	Good	VT on day 2 after mexiletine electively withheld
J H	48	M	71	VT VES	4 0	Good	Exercise tolerance test before therapy showed VT + + ETT × 2 since No significant arrhythmia
Mean	46 [illegible]				10 0		

Table V Plasma concentrations of mexiletine in relation to therapeutic and toxic effects

Group	*Etiology of arrhythmias*	*No of patients*	*Mean minimum therapeutic concentration and range (μg/ml)*	*Mean toxic concentration (μg/ml) (symptoms severe enough to decrease or stop therapy)*
A	Myocardial infarction	11	1 [illegible] (0 9 2 6)	2 1 (1 5 3 0)
B	Ischemic heart disease	7	1 3 (1 2 1 6)	2 2 (1 [illegible]-2 8)
C	Idiopathic	6	1 2 (1 0 1 2)	1 9 (1 8-2 0)
Total and mean of groups		[illegible]4	1 4 (0 9 [illegible] 6)	[illegible] 1 (1 5 3 0)

Table I Result of oral mexiletine therapy in 24 patients with ventricular arrhythmias

Group	Etiology of arrhythmias	No of patients	Control of ventricular arrhythmias		
			Complete disappearance	Partial disappearance	Failure
A	Myocardial infarction	11	10	1	–
B	Ischemic heart disease	7	4	2	1
C	Idiopathic	6	5	1	–
Total		24	19 (79%)	4 (17%)	1 (4%)

Table II Summary of oral mexiletine therapy Group A Myocardial infarction, mean age 50 9 years mean duration of therapy 3 7 months

Initials	Age	Sex	Weight (kg)	Arrhythmia	Duration of therapy (mo)	Control	Comments
A I	42	M	68	VES	4 6	Good	VT recurred on third day after mexiletine electively withheld
P W	58	M	85	VT VES	3 4	Good	
T C	52	M	64	VT VES	1 2	Good	Tremor bad Mexiletine stopped Could not tolerate effective dose
J I	42	M	76	VES	2 5	Good	
P McC	56	M	70	VT VES	1 5	Good	
J M	32	M	66	VF VT VES	10 5	Good	Dose increases needed? Tolerance Mild dizziness once at 3 μg per milliliter
C C	73	M	67	VF VES	1 3	Good	Electively stopped 6 weeks after myocardial infarction Sudden death 3 days later
J D	47	M	60	VES VF	6 8	Good	
F A	57	M	81	VT VF	2 8	Fair	Tremor bad necessitating dose reduction Sudden death 4 days later
W C	63	M	80	VES	4 2	Good	
A A	39	M	77	VES	1 6	Good	

while on continuous ECG taping (e g Fig 5) and the arrhythmias were promptly controlled when mexiletine was recommenced In addition two outpatients died suddenly a few days after the dose of mexiletine was reduced or stopped and it is possible that the arrhythmia recurred

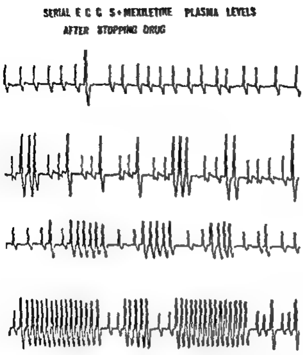
Examples of the efficacy of oral mexiletine are seen in Figs 2 to 5

Dosage and plasma concentrations of mexiletine Most patients tolerated a daily dose of 750 mg daily (250 mg every 8 hours) which produced relatively stable plasma concentrations of between 1 0 and 1 5 μg per milliliter (mean 1 3) Our findings confirm previous studies which showed that the effective plasma concentration lies usually within this range, though in some patients daily doses of up to 1 500 mg per day giving plasma levels of up to 3 0 μg per milliliter were needed Surprisingly low plasma levels were occasionally found in outpatients This was due to failure to take the drug since much higher plasma concentrations were achieved when these patients were admitted to hospital The mean minimum therapeutic plasma concentrations are summarized in Table V

Plasma concentrations were higher than expected in relation to the dose given in patients with congestive heart failure

Mild tolerance was suggested (e g Fig 5) but was overcome by adjustment of dosage

Toxicity In eight patients toxic symptoms were observed though in only three were these severe enough to stop therapy permanently and reduction of the dose was necessary in a further four



HOURS AFTER STOPPING MEXILETINE	PLASMA LEVEL mg/100ml
3 5	1 86
20	0 95
30	0 61
47	0 32

Fig 3 Serial ECG s and plasma levels after stopping mexiletine therapy

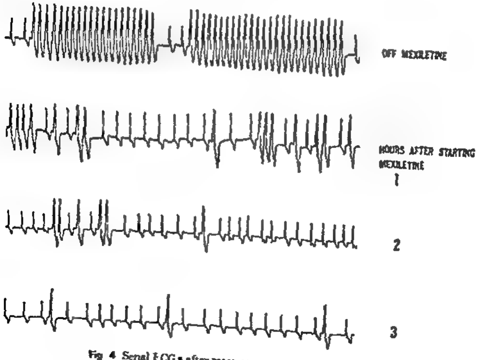


Fig 4 Serial ECG s after recommencing mexiletine therapy

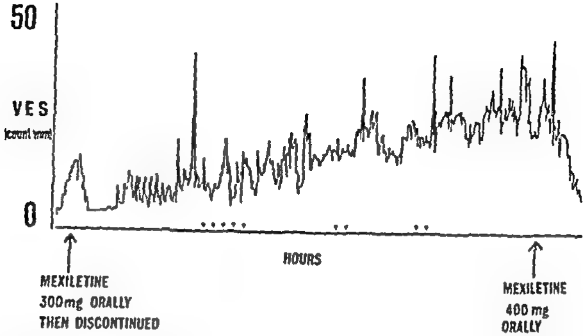


Fig 2 Computer write out demonstrating increasing incidence of ventricular extrasystoles when regular mexiletine therapy was discontinued for 47 hours followed by sharp decrease after recommencing therapy

Table VI Toxicity of oral mexiletine

Group	*Etiology of arrhythmias*	*No of patients*	*No with toxic symptoms*	*Symptoms**		
				Mild	*Moderate*	*Severe*
1	Myocardial infarction	11	3	1	1	1
2	Ischemic heart disease	7	3	–	2	1
3	Idiopathic	6	2	–	1	1
	Total	24	8	1	4	3
			(33%)	(4%)	(17%)	(12%)

*Moderate requiring dose reduction severe requiring cessation of therapy

patients (Table VI) Toxic manifestations were remarkably uniform in their presentation The first sign was almost invariably a fine tremor of the hands This became more marked with increasing concentrations of mexiletine and was then accompanied by dizziness, blurred vision and occasionally nausea Frail old female patients seemed particularly susceptible The mean toxic concentration in each group is summarized in Table VI The range was from 1 5 to 3 0 μg per milliliter, with a mean value of about 2 μg per milliliter in each group although there were insufficient instances for this figure to be more than an approximation

Regular hematological and biochemical investigations showed no abnormalities In particular, a positive serum ANF never developed Three cases had a strongly positive test before starting mexiletine (two had previously been on procainamide) and in all three this reverted to negative while on mexiletine

Discussion

A significant relationship between sudden death and previously observed ventricular arrhythmias has been demonstrated by many recent investigators[9-13] Although a direct relationship has not been proved this is probable especially in patients with ischemic heart disease[9-11] It is unclear whether the incidence of sudden death is reduced by effective antiarrhythmic therapy but in such circumstances treatment is often considered

Currently available long term antiarrhythmic agents have serious disadvantages Procainamide has to be given regularly every 3 to 4 hours and serious adverse reactions are common[14-16] Quinidine is unpopular as a prophylactic agent

tological and biochemical screening revealed no problems of toxicity

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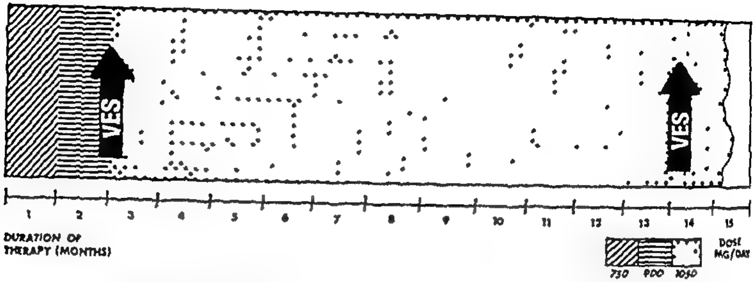

Fig 5 Mexiletine long term oral therapy group 3 idiopathic ventricular arrhythmias J B 41 years old 100 3 kilograms Typical treatment scheme showing increase in dose probably due to tolerance and recurrence of VES when mexiletine was temporarily withdrawn

because of the frequency of toxic reactions—gastrointestinal disturbances are common and there is an appreciable mortality rate from asystole and VF [17] Diphenylhydantoin has not proved particularly effective [18] Beta adrenergic blocking drugs are relatively ineffective and tend to depress cardiac contractility [19, 20]

Oral mexiletine is effective in the short term treatment of ventricular arrhythmias The present studies suggest that it is also effective over periods of months adequate plasma levels are readily maintained and it is generally well tolerated with no hematological or biochemical evidence of toxicity

The effectiveness of mexiletine in this study is difficult to assess since the series is small there were no control data in many patients and observations made during initiation of therapy are not easy to interpret because many patients had previously been on other antiarrhythmic therapy or were suffering from an unstable condition such as a recent myocardial infarction Nevertheless apparently satisfactory control was achieved in 20 out of 24 patients—checked on repeated outpatient visits The six patients with idiopathic ventricular arrhythmias form a particularly convincing group They had had no other recent antiarrhythmic therapy they tended to be more stable in their initial presentation and the continuous ECG tapes indicate a good response to therapy in all The redevelopment of severe ventricular arrhythmias in five patients after withdrawal and during continuous ECG taping is impressive

The incidence of toxic symptoms in eight patients seems at first rather high However the duration of mexiletine therapy was over 10 patient years and yet symptoms were severe enough to necessitate termination of therapy in only three patients These three, in fact, had relatively low dosages and plasma levels and differed from the other five most of whom suffered from ventricular arrhythmias refractory to other therapy and may have required higher concentrations for effective control There is a rather small margin between therapeutic and toxic plasma concentrations of mexiletine but provided the patient can be stabilized on the correct dosage there should be little difficulty in long term therapy There was no evidence of cardiovascular, hematological, or biochemical toxicity, and the lack of development of positive antinuclear factor with reversion from strong positive to negative tests during treatment is encouraging

These results suggest that mexiletine has considerable potential in the long term treatment of ventricular arrhythmias

Summary

Twenty four patients with ventricular arrhythmias were treated with oral mexiletine for periods of from one to 16 months (total 10 4 patient years) In 19 patients arrhythmias were satisfactorily controlled and plasma levels previously shown to be within the therapeutic range were maintained on an 8 hourly regimen The drug was well tolerated in most patients and regular hema

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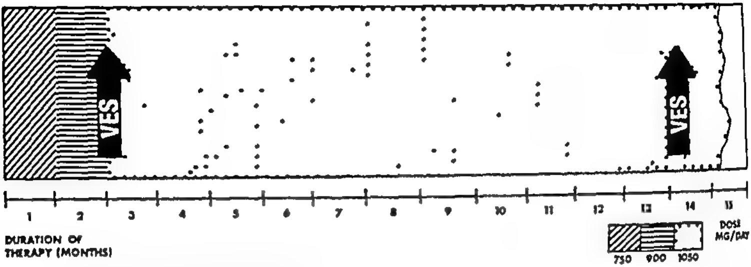

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Cardiac conduction abnormalities produced by chronic alcoholism

Philip O Ettinger M D
Michael Lyons, M D
Henry A Oldewurtel
Timothy J Regan, M D
Newark N J

Cardiac conduction abnormalities and rhythm disturbances are common clinical findings in alcoholic cardiomyopathy[1,2] Bundle branch block, varying degrees of atrioventricular block, focal block resembling infarction patterns, atrial and ventricular arrhythmias have all been reported in patients with this syndrome The specific etiology of these alterations, however has remained speculative as the excessive use of alcohol is frequently accompanied by malnutrition and the effects of possible associated coronary artery disease and electrolyte imbalance have been difficult to exclude Several clinical and laboratory studies have indicated a direct depressant effect of acute and chronic ingestion of ethanol upon myocardial function[3,4] More recently, ultrastructural changes in myocardium have been shown to follow chronic administration of pure ethanol to dogs[5,6] and ethanol beer and wine to mice[7] To investigate the chronic effects of ethanol upon cardiac conduction ethyl alcohol was added to the drinking water of 11 healthy male mongrel dogs whose dietary intake included adequate amounts of protein and vitamins Cardiac conduction and morphology were evaluated after 7 to 33 months of ethanol intake

From the Departments of Medicine and Pathology College of Medicine and Dentistry New Jersey Medical School Newark N J

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Reprint requests Philip O Ettinger M D New Jersey Medical School Department of Medicine 100 Bergen St Newark N J 07103

Methods

Healthy young male mongrel dogs weighing between 20 and 35 kilograms and 2 to 3 years of age, were selected for inclusion in a chronic study of experimental alcoholism Each was housed in an individual cage and was clinically free of disease during 1½ to 2 months of observation before admission to the study Blood samples were negative for heartworms hematocrit and serum proteins were normal

Both the chronic experimental group and all normal control animals evaluated acutely during the same period of time were fed approximately 28 calories per pound All animals initially received a diet consisting of a mixture of meat and meal which provided 26 per cent of calories as protein 12 per cent fat and 62 per cent carbohydrate Following replacement of 36 per cent of calories by ethanol, the corresponding values provided by solid food in the alcoholic group were 16 6 per cent protein, 7 7 per cent lipid and 39 7 per cent carbohydrate, which met the minimum standards for maintaining a normal nutritional state[8] After several weeks of progressively increasing doses of alcohol the chronic ethanol animals were provided with alcohol for 6 days per week On the seventh day no alcohol was fed and the diet was the same as in controls The dogs almost invariably consumed all of the solid food provided The ethanol (U S P *) was administered by dilution in drinking water as a 15 to 30 per cent solution for the first month and 40 per cent thereafter The actual intake per animal was estimated each day by measuring the residual

*Acquired from U S Industrial Chemicals Company Division of National Distiller & Chemical Corp New York N Y

ethanol solution when present The intake of each animal remained relatively constant but the fraction consumed varied from one third in some animals to the entire administered dose in others Some of the ethanolic animals regularly appeared intoxicated manifested by staggering and falling while others were somnolent Both groups received a vitamin supplement twice weekly Folbesyn intramuscularly (Lederle Co Pearl River New York*) This weekly vitamin dosage included thiamine HCl 5 mg riboflavin ■ mg niacin 35 mg pyridoxine HCl 2 5 mg ascorbic acid 150 mg B_{12} 2 µg sodium pantothenate 5 mg and folic acid 1 5 mg Two separate venous blood samples were taken at the onset of the study and then again at 2 month intervals to determine hematocrit serum protein[9] and albumin[10] At the terminal study blood samples were taken for analyses of vitamins of the B series as well as vitamins A C and E (performed in the laboratory of Dr Herman Baker) These values were not significantly different in alcoholic and control animals[4]

Animals were studied terminally from 7 to 33 months after onset of alcoholism (One chronic dog died suddenly after 17 months his high speed *electrocardiogram* (ECG) was recorded at rest on the day before death and ■ included in the appropriate calculations) Varying times for putting the animals to death were chosen arbitrarily in order to evaluate the effects of increasing duration of ingestion After premedication with morphine sulfate (3 mg *per kilogram*) anesthesia was induced with 12 mg *per kilogram* of intravenous sodium *pentobarbital* Following endotracheal intubation and placement in a left lateral position respiration was maintained with the use of a mechanical respirator to maintain arterial saturation and pH within the normal range Surgical exposure of the cervical and femoral regions exposed jugular carotid and femoral vessels for catheterization *An electrode* catheter of the Damato or Castillo type (Electro Catheter Corp Rahway N J) was preshaped by curving the distal 5 to 7 cm into a loop with a diameter of 1.5 cm Under fluoroscopy this catheter uncoiling into a J shape was passed via either carotid artery into the anterior region of the aortic root immediately above the aortic valve to record a His bundle electrogram[12, 13] Bipolar recordings with the tip and adjacent electrode were made with a multiple electrode switch box (Electronics for Medicine Inc White Plains N Y) The output of the switch box was led into the A C input of an ECG preamplifier filtered at 40 to 500 c.p.s and recorded on photographic paper at a speed of 200 mm per second with an Electronics for Medicine recorder A second similarly curved electrode catheter was passed via the other carotid artery into the midportion of the left ventricle and directed anteriorly to record from a branch of the peripheral Purkinje radiation of the left bundle branch[13, 15] The bipolar electrogram from this site was recorded simultaneously with the His bundle electrogram To pace the heart a third bipolar electrode catheter was positioned at the junction of the superior vena cava and right atrium via the jugular vein After recording of the electrograms at rest atrial pacing raised the heart rate at 20 to 30 b p m increments to 200 b p m or until Wenckebach A V block occurred with the use of a Medtronic model 5737 pacemaker

In several animals automaticity was evaluated by attempting to induce the repetitive ventricular response phenomenon described by Lown and associates[16] To accomplish this the electrode catheter in the left ventricle was placed in contact with the ventricular wall Utilizing the synchronizing mode of the pacemaker a twice threshold stimulus was gradually allowed to mount the T wave of the previous normal beat until it failed to produce an extrasystole A repetitive ventricular response however was not seen in any animal

Arterial pressure was monitored via the femoral artery After completion of electrophysiologic measurements the electrode catheters were withdrawn and evaluation of myocardial function and metabolism was begun These are the subjects of a separate communication[11] Resting left ventricular pressure volumes and stroke outputs were within normal limits in these animals, although mean left ventricular end diastolic pressure was 9 mm Hg in the alcoholics compared with 6 mm Hg in controls ($P<0.05$)

At the conclusion of the study rapid thoracotomy and pericardiotomy exposed the heart which was fibrillated by application of iced Ringer s lactate The heart was quickly removed in toto and placed in iced Ringer s solution Ventricular muscle and Purkinje strands for electron microscopy were taken within 1 minute and diced in cold glutaraldehyde to prevent fixation artifact (see

*Generously supplied by Dr William Sween ■ f Lederle Company

Table I Electrophysiologic data in alcoholic and normal dogs

	Duration of ingestion (mo)	Heart rate (b p m)	PRc (msec)	H Q (msec)	H a (msec)	QRS (msec)	QTc (msec)	N
Alcoholic dogs								
Group 1 (< 1 yr)	8 6 ± 0 4	133 ± 21	139 ± 10	26 6 ± 1 3	16 1 ± 2 3	64 6 ± 2 3	332 ± 22	5
P		NS†	NS	NS	NS	NS	NS	
Group 2 (> 1 yr)	19 2 ± 3 0	84 ± 7	151 ± 9	34 7 ± 2 8‡	22 8 ± 3 9‡	80 2 ± 3 8	368 ± 15	6
P		<0 001	NS	<0 001	<0 001	<0 001	NS	
All	14 4 ± 2 3	106 ± 12	145 ± 6	30 6 ± 2 0	19 5 ± 2 4	73 1 ± 3 2	352 ± 14	11
P		<0 01	NS	<0 02	<0 01	<0 01	NS	
Normal dogs		106 ± 7	157 ± 4	26 0 ± 0 7	13 0 ± 0 8	62 1 ± 2 3	336 ± 9	30

I values are for comparison with normal group
†NS = not significant
‡H Q and H a values in Group 2 are calculated for five animals only as one died before the final study

below) To compare animals of different size the entire left ventricular free wall and septum were cut away from the remainder of the heart and weighed The left ventricular weight which included all fragments of left ventricular muscle was then divided by body weight to yield a heart weight index expressed in grams of left ventricle per kilogram of body weight These weights were compared with corresponding data from a normal group The coronary arteries were examined grossly and did not show occlusive disease in any animal

Full thickness segments of myocardium from the apical region of the left ventricle were taken from all alcoholic dogs and from two normal animals for light and electron microscopic evaluation The tissue for light microscopy was placed in 10 per cent neutral buffered formalin later the fixed, embedded specimen was cut transversely to show endocardium at one edge and epicardium at the other Different slices in all animals were stained with hematoxylin and eosin, periodic acid-Schiff (PAS) and Alcian Blue at pH 3 65 and 8 5 Trichrome stain was used to locate interstitial collagen In a few animals frozen sections of myocardium were stained with Oil Red O For electron microscopy, a transmural segment was cut into outer middle and inner thirds and each of these was then separately diced in 4 per cent cold glutaraldehyde The pieces were later fixed in osmium tetraoxide embedded in Epon, and stained with lead and uranyl acetates These were sectioned on an LKB microtome and examined with a model 9 S Zeiss electron microscope Fascicular conduction tissue removed as free running false tendons from the endocardial surface of the left ventricle, was cut into several small pieces and similarly prepared for electron microscopy

In two alcoholic animals a block of tissue including the low right atrium, the base of the tricuspid valve, and that portion of the left ventricle surrounding the membranous septum was taken for examination of the proximal ventricular conduction system by light microscopy This block was sectioned in a transverse plane from the lumenal aspect of the right ventricle in an anteroposterior direction Five or six sequential segments were each embedded and sectioned on its superior face and microsections were stained with hematoxylin and eosin, Alcian Blue and PAS

The onset of the first rapid component of each His and bundle branch impulse was taken as its onset and the intervals measured were from the beginning of the P wave to the His bundle impulse (P H), His to anterior *false tendon* (H a), the PR interval the total QRS duration, and the QT interval Corrected values for PR and QT (PRc and QTc) were calculated by dividing the observed value by the square root of the R R interval (in seconds) The maximum QRS duration observed in the three standard leads was utilized in both control and chronic ethanol animals For electrophysiologic comparisons data from 30 normal male mongrel dogs in the same age range of 2 to 4 years were utilized For determination of heart weight an additional 48 normals in the same total body weight range were included

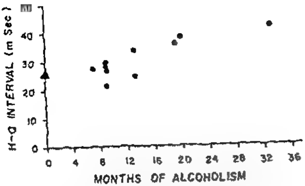


Fig 1 H Q duration as a function of the duration of alcoholism The mean of 30 normal dogs is represented by the triangle on the ordinate A more prolonged H Q with extended drinking was observed

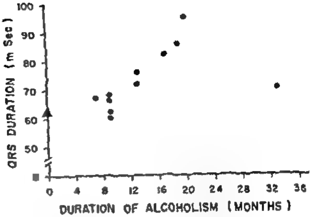


Fig 2 QRS duration as a function of duration of alcoholism The mean of the normal group is represented by the triangle on the ordinate

To determine if ethanol can alter cardiac conduction acutely His and bundle branch recordings were made in two normal anesthetized dogs before and during a 2 hour infusion of ethanol 0 1 mg per kilogram per minute This dose induces blood alcohol levels consistent with clinical intoxication in man[4]

Statistical calculations were performed by computer using standard statistical methods for small samples All values are expressed as means ± standard errors Mean values for the alcoholic animals were compared with means of the normal group using Student s t test for unpaired means Comparison of data in the same animal in differing physiologic states was made using the t test for paired values

Results

Electrophysiologic data in the 11 chronic animals studied are presented in Table I Cardiac conduction abnormalities were present predominantly in those animals with more than 1 year of ethanol ingestion Consequently five animals with less than 12 months of alcoholism and six of longer duration were arbitrarily tabulated separately as Group 1 (short term) and Group 2 (long term) alcoholics the means for the entire group are also given and both subgroups and the full number are compared statistically with the normal dogs

Heart rate Heart rate was slower in the alcoholic animals than in the normals 106 ± 12 b p m compared with 160 ± 7 (P<0 01) This rate difference was primarily due to the fact that the chronic animals representing a large investment of funds and time were instrumented earlier in the day sooner after anesthesia A real rate effect cannot be entirely excluded however To assure that heart rate alone did not affect the electrophysiologic measurements a comparison was made of PRc H Q QRS and QTc values in our normal dogs with rates below 100 b p m and above 100 b p m No differences were found

Corrected PR interval (PRc) The corrected PR interval was not different in the alcoholics as compared with normal dogs

H Q intervals The H Q interval (or H V the shortest conduction time from the bundle of His to the onset of ventricular activation) was 31 ± 2 msec in the 11 alcoholics compared with 26 ± 1 msec in normals (P<0 05) While the Group 1 animals were not significantly different from normal Group 2 showed a mean H Q of 35 ± 3 msec (P<0 001) in comparison with controls Changes in H Q were time and/or dose related as demonstrated in Fig 1 where H Q is seen to increase progressively with duration of alcoholism The one long term animal exhibiting no increase in H Q had a relatively low intensity duration factor because he ingested only an estimated one third of the daily ration H Q was not altered during acute ethanol infusion in the two normal animals

Bundle branch conduction times Conduction time from His bundle activation to the left bundle branch was slightly prolonged while time from the bundle impulse to the onset of ventricular depolarization was normal Because of possible differences in placement of the left ventricular endocardial electrodes from animal to animal it

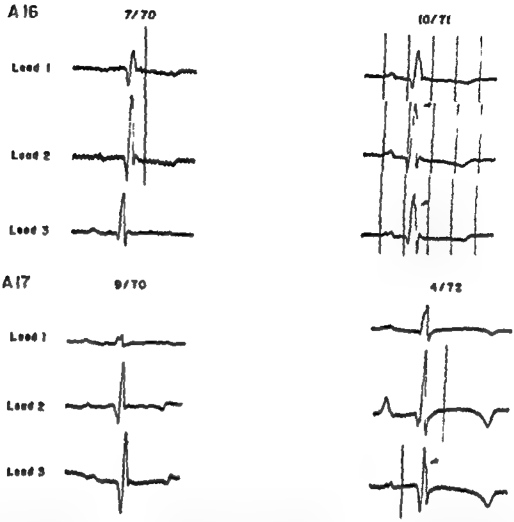


Fig 3 High-speed high frequency ECG s of two alcoholic dogs recorded sequentially during the period of alcohol ingestion The earlier ECG in each is control (The three standard leads were not recorded simultaneously) QRS prolongation of moderate degree was associated with development of high frequency notching (later recordings) in both (see arrows) Minor differences in QRS T configuration are related to position as ECG s were obtained sitting or lying down when awake but only lying down in the final study Mean QRS and T wave vectors are not usually similarly directed even in normal dogs Paper speed 200 mm per second frequency response 0 1 to 2 000 c p s.

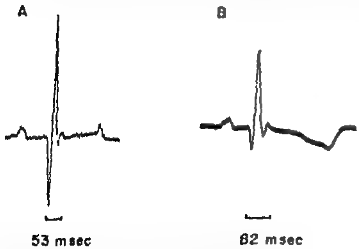


Fig 4 Increased QRS duration in a dog (A25) drinking for 17 months Left standard ECG Lead II 1 month after starting alcohol QRS duration 53 msec Right QRS 82 msec in same lead 16 months later No notching was seen in this ECG A25 died suddenly on the day following the last recording no H Q was obtained Because of different heart rates and electrical standardizations QRS voltage QT and PR are not directly comparable Paper speed 200 mm per second

is not considered that these findings specifically indicate localization of a proximal Purkinje block

QRS duration QRS duration was also prolonged in the alcoholics in comparison with normals This difference was most apparent in the long term animals where the mean QRS measured 80 ± 4 msec compared with 62 ± 2 msec in normals ($P<0.01$) The mean QRS of all alcoholics was significantly longer than control, but the short term animals were not responsible for this difference (Fig 2) QRS was not prolonged in the two normal dogs during acute ethanol infusion High frequency, high speed ECG s recorded at rest were obtained in two animals, A16 and A17, and are shown in Fig 3 A16, which had 13 months ingestion but regularly drank only one third of his alcohol, showed slight prolongation of QRS A17, with 19 months of 100 per cent ingestion, showed a definite increase in

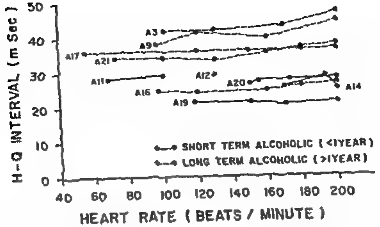


Fig 5 H Q interval during atrial pacing Short and long term animals are identified Although the majority of animals showed little change the two most abnormal (and longest term) dogs increased H [illegible] by approximately 15 per cent

QRS duration In both animals new high frequency notching of the QRS was observed In one 17 month animal (A25) QRS prolongation from 53 to 82 msec was observed in ECG s taken 16 months apart (Fig 4)

QTc interval The rate corrected QT interval QTc was 352 ± 14 msec in the alcoholic group compared with 336 ± 9 msec in normals (P = NS) In the long term animals QTc was 368 ± 15 msec a value approaching significance (0 1>P>0 05)

Atrial pacing studies During right atrial pacing a general tendency was noted for H Q to increase slightly (Fig 5) These slight increases were of the general order of 10 per cent but did not occur in all animals Almost every animal could be paced to 200 b p m even when Wencke bach block occurred at lower rates a slower increase in pacing rate eventually allowed pacing up to maximum rate We have observed a 5 to 10 per cent prolongation of H Q during atrial pacing to 200 b p m in some normal dogs

Left ventricular weight whole body weight and left ventricular weight index were not signif icantly different in alcoholics compared to normal dogs (Table II) Mean body weight did not change in either group during the course of their alcoholism and hematocrit remained in the normal range

Trichrome-stained sections of myocardium did not reveal a collagen increase Oil Red O indi cated a modest increase in lipid droplets The most prominent abnormality observed in the light microscope was an accumulation of Alcian Blue-positive material throughout the ventric

Table II Left ventricular weight and weight index in alcoholic and normal dogs

	LV weight (Gm)	*Body weight (kg)*	*Heart weight index (Gm/kg)*	*N*
Alcoholic dogs				
Group 1 (< 1 yr)	131 ± 11	25 ± 1	5.2 ± 0.5	5
Group 2 (> 1 yr)	98 ± 11	21 ± 3	4.8 ± 0.3	6
All	113 ± 9	24 ± 2	4.9 ± 0.3	11
Normal dogs	113 ± 3	23 ± 1	4.8 ± 0.1	48

P = NS for all comparisons.

ular myocardium A recent report from this labo ratory demonstrated this histologic change [11] The material appeared to be extracellular in location and was associated with increased extracellular material on electron microscopy however the exact distribution and composition of the stained substance is not yet clear As Alcian staining was maximal at pH 3 it may be of acid mucopolysac charide composition The Alcian staining was also concentrated in the annulus of the tricuspid valve in the A V nodal area and in the proximal portions of the main conducting fascicles

On electron microscopy the cardiac myofibrils and mitochondria were normal in appearance although there were occasional groups of large mitochondria with normal internal structure The sarcoplasmic reticulum was dilated in many areas in comparison with the normal heart and glycogen granules were generally increased in number (Figs [illegible] and 7) Of importance from the

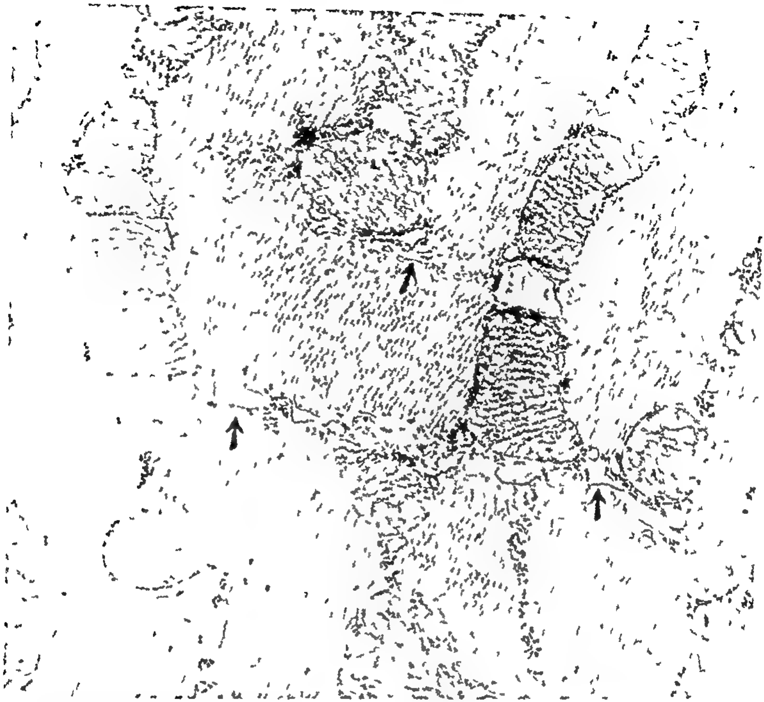


Fig 6 Ventricular myocardium of normal dog Sarcoplasmic reticulum (arrows) mitochondria and myofibrils are normal (Original magnification ×9 500 final ×38 000 Reduced by one third)

viewpoint of conduction abnormality were alterations in the intercalated discs (Figs 8 to 10) In many sections of ventricular muscle, localized dilatation and even cystic changes were apparent in the nonspecialized regions of the disc Desmosome regions and nexus portions of the disc appeared normal Intercalated discs observed in the false tendon sections also demonstrated dilatations in the undifferentiated region similar to changes observed in working myocardium (Fig 11)

Discussion

The ECG in patients with alcoholic cardiomyopathy shows a variety of abnormalities [1, 2, 19, 20] Ventricular and atrial arrhythmias are common particularly isolated extrasystoles and atrial fibrillation Pathologic Q waves suggesting myocardial infarction have been attributed to fibrosis [2] Flowers and Horan [9] have indicated that absence of a septal Q wave in Leads I aVl and V_6 has a 40 per cent incidence in cardiomyopathy In hospitalized patients with primary myocardial disease left axis deviation left and right bundle branch block and pathologic Q waves were also common [10] Unfortunately alcoholic patients may be malnourished, and the relative effects of alcohol and other clinical factors are difficult to ascertain Demonstrable malnutrition is not an invariable accompaniment Neville and asso

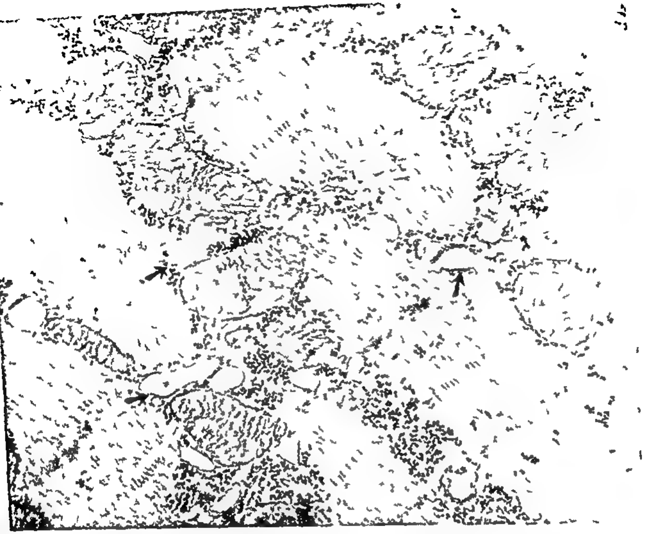
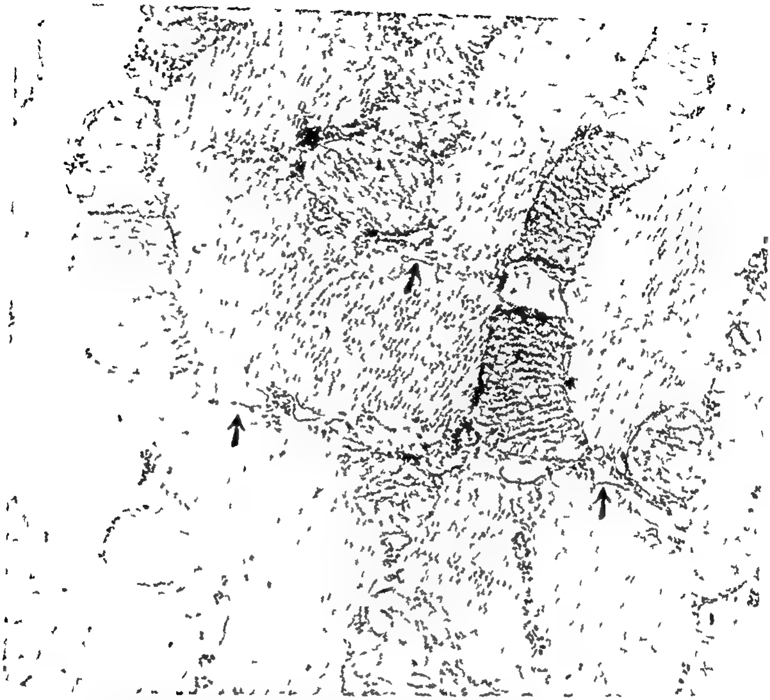


Fig. 7 Ventricular myocardium of alcoholic dog. Tubules are dilated (arrows) although mitochondria and myofibrils appear normal. Glycogen granules are prominent. (Original magnification ×9,500 final ×38 000 reduced by one-third same as in comparison Fig 6.)

ciates[4] observed a relatively low incidence of vitamin deficiency in a group of lower middle class alcoholics and both Evans[1] and Brigden and Robinson[2] stressed the frequency of corpulence in alcoholics with cardiomyopathy seen in London

The present study was designed to evaluate the effects of ethanol alone upon the conduction system of the heart Demonstration of both H Q and QRS prolongation relating to the intensity and duration of alcoholism suggests that ethanol ingested chronically has a specific toxic effect upon myocardial tissues including those of the ventricular conduction system This toxicity is cumulative and is not produced by acute alcoholism or short term alcoholism As left ventricular weights and weight indices (Table II) were not different in alcoholics as compared with normals cardiac enlargement and/or hypertrophy could not have accounted for these findings. None of our animals developed bundle branch block perhaps because of relatively short duration of chronic ingestion It is unusual to observe clinical alcoholic cardiomyopathy in man when the duration of addiction is less than 10 years

Although no arrhythmias were observed in these animals while under anesthesia they were not monitored electrocardiographically while awake Current understanding of arrhythmias suggests that conduction delay may play an important role in their production by facilitating re-entry Many reports of histologic evaluation of the heart in human cardiomyopathy[22,24] and



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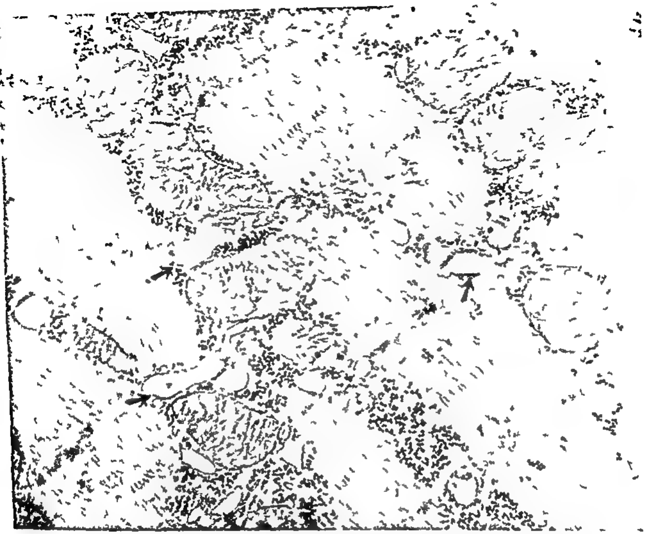

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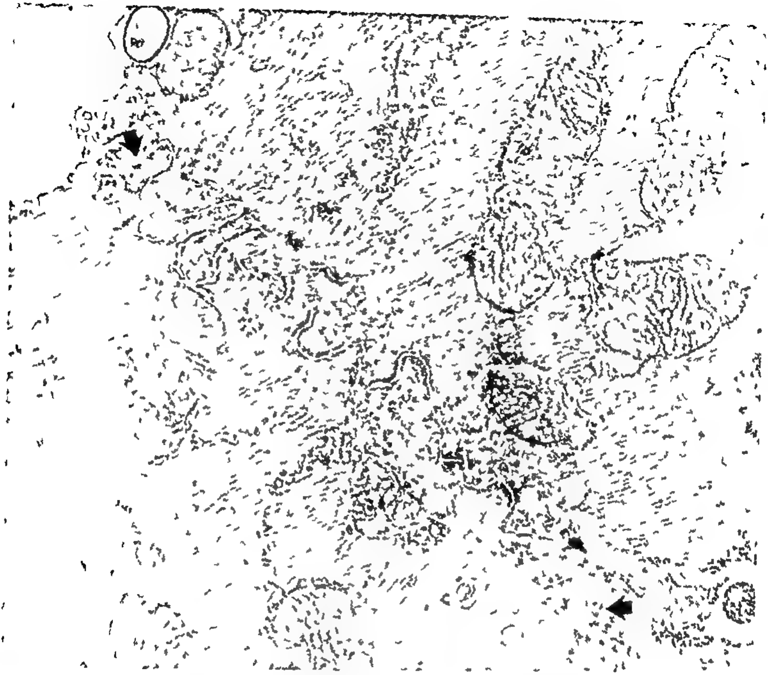

Fig 8 Electron photomicrograph of intercalated disc normal dog The disc crosses the field from upper left to lower right (arrows) (Original magnification ×9 500 ×38 000 final Reduced by one third)

following ingestion of alcohol by animals[7, 25] emphasize the patchy and variable distribution of lesions If conduction delays are similarly distributed then a basis for development of arrhythmias may exist In this regard, several of our chronic animals died suddenly and unexpectedly during the many months of observation

Experiments in normal animals indicate that acute ECG effects of ethanol are induced only by serum concentrations in the range of 600 to 1 000 mg per 100 ml or higher[26, 27] and it has been suggested that hypoxia secondary to respiratory depression is required to induce rhythm disturbances under these circumstances[28] In a previous study from this laboratory, however ventricular ectopic beats began to appear after only ½ to 2½ hours of ethanol administration[4] Ethanol has been shown to shorten the action potential of atrial muscle,[3] which might predispose to arrhythmia although only at concentrations much higher than those ordinarily observed in alcoholic man In another investigation of chronic alcoholism in rats[30] a tendency toward arrhythmias was apparent While applicability of animal studies to human disease may be limited similarity between them and the apparent tendency to sudden death in alcoholics[31, 32] invites speculative comparison

The relative importance of fascicular (H Q) and intramural (QRS) conduction delay to ar

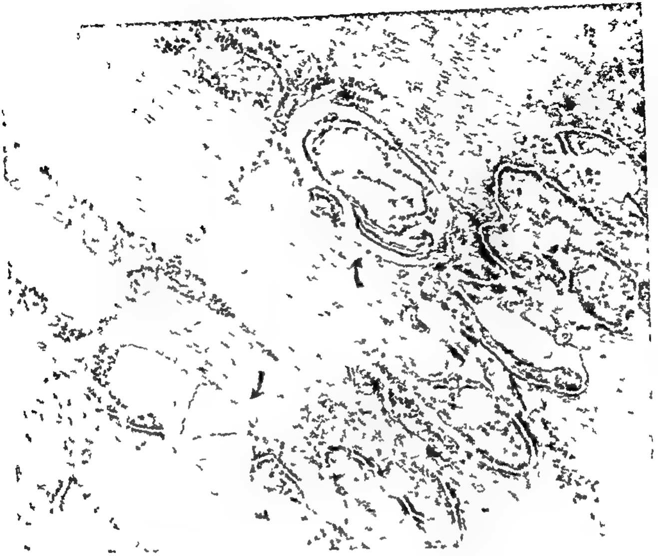

Fig. 9. Intercalated disc of alcoholic dog. Cystic areas of dilatation of undifferentiated regions are apparent (curved arrows). A nexus (straight arrow) appears normal. (Magnification ×9,500; ×47,500 final. Reduced by one third.)

rhythmia is not known. In either case, the localized conduction heterogeneity might allow reentry to occur. High frequency notching in the ECG's of our chronic dogs suggests that discrete regions of conduction slowing may be present.

We observed two types of structural changes which may be associated with altered conduction: accumulation of Alcian Blue staining interstitial material and disruption of portions of the intercalated discs. The Alcian Blue positive interstitial material was present throughout the myocardium but localized heavily in the region of the tricuspid valve ring and the summit of the ventricular septum, directly infiltrating the main conducting fascicles.

Since the intercalated disc is believed to allow electrotonic coupling between cells,[3] structural abnormalities there might induce conduction delay. As noted in a recent monograph,[3] controversy exists about the electrical resistance of the intercalated disc: some attribute to it a high[35, 36] and others a low[37] electrical resistance. Our results indicate that dilatation and swelling of the undifferentiated regions with visibly normal nexus regions and desmosomes are associated with prolonged conduction. If the morphologic changes in the intercalated discs of our dogs are the cause of conduction disturbance, then the view that the nexus region represents the area of lowest electrical resistance is not supported by

Fig 10 Higher magnification (×106 400 reduced by one third) of section of intercalated disc alcoholic dog Nexus (small arrow) desmosome (thick arrow) and undifferentiated region (thin arrowhead) are indicated Fine structure of the nexus and desmosome is normal Edge of a mitochondrion is seen in upper left corner

our data, in which conduction is abnormal despite visibly normal tight junctions

Dilatation of the undifferentiated region of the disc is not a specific finding It has been observed in a variety of congenital and acquired cardiac diseases and toxic conditions in man and experimental animals These have been recently summarized[37] and will not be reviewed here To our knowledge, no previous study had correlated this finding with a demonstrated conduction disturbance

The permanence of the physiologic and anatomic disturbances noted here cannot be determined from the present investigation As reversion of rhythm disorders and some reduction of cardiomegaly is seen in patients with cardiomyopathy following prolonged bedrest with abstinence,[38] some of the conduction abnormalities might resolve with time While these pathologic features may not be specific for ethanol, they nevertheless are consistent with a cumulative toxic effect of this agent, apparently independent of diet

Summary

While conduction disturbances and arrhythmias are seen frequently in alcoholic cardiomyopathy, the specific relationship of these changes to ethyl alcohol has been unclear To investigate the long term effects of ethanol upon cardiac conduc

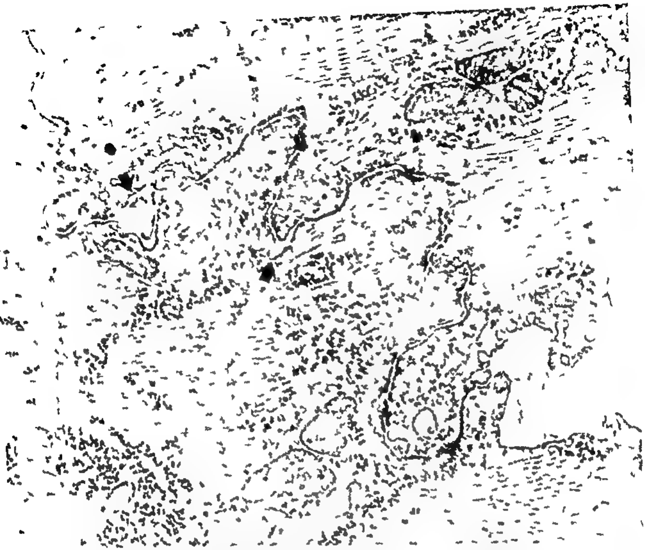

Fig 11 Electron photomicrograph of intercalated disc from false tendon Purkinje cell of alcoholic dog Areas of cystic dilatation of the undifferentiated region are indicated by arrows Nexus and desmosome regions are virtually normal (Original magnification ×9 500 final ×39 000 Reduced by one-third)

tion alcoholism was induced in 11 male mongrel dogs for 7 to 33 (mean 14 4) months by feeding up to 36 per cent of total daily calories as ethanol while adequate nutrition was maintained His and left bundle branch electrograms in the intact anesthetized animals were recorded along with high speed high frequency ECG's While resting left ventricular pressures volumes and stroke outputs were normal H Q time was prolonged in the alcoholic animals drinking *for longer than one year* (35 ± 3 msec normals 26 ± 1 msec—$P<0\,001$) QRS widening (to 80 ± 4 msec) was also evident *after one year* as compared with normals (62 ± 2 msec—$P<0\,001$) and both H Q and QRS alterations correlated with duration of intake These changes were less after shorter ingestion periods could not be reproduced in normals by acute ethanol infusion and were not associated with ventricular hypertrophy inflammation or necrosis No abnormalities of atrial conduction were noted Morphologic correlates of the conduction abnormalities included accumulation of Alcian Blue-positive interstitial material as well as dilatation and localized swelling of the nonspecialized region of the intercalated discs in ventricular muscle and Purkinje fibers Thus prolonged ethanol intake in the absence of evident malnutrition resulted in demonstrable intraventricular conduction abnormalities and morphologic alterations which were

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Case reports

Progressive improvement of His Purkinje conduction during recovery from catheter-induced heart block

Rafael Levites M D
Mohammed Toor M D
Jacob I Haft M D*
New York N Y

Wenckebach block (Mobitz Type I) is characterized by progressive lengthening of the PR interval until a P wave is not conducted In the majority of patients this phenomenon is due to block at the A V node and is manifested by gradual prolongation of the AH interval followed by block above the His bundle on His bundle electrography (HBE) [1] The usual type of intermittent A V block in the conduction system below the A V node is Mobitz Type II block (sudden non conduction of a P wave) Prior to block the HV interval is constant and there is usually no gradual prolongation of the HV interval before failure of conduction Hence conduction through the intraventricular conduction system (IVS) usually acts as an all or none phenomenon [1] Although there have been a number of reports of Wenckebach periodicity within the IVS suggested by electrocardiographic (ECG) studies[7] and documented by HBE it is still not unequivocally accepted that the conduction rate through the Purkinje system can vary

During recording of HBE gradual changes of conduction velocity through the IVS were observed in a patient with left bundle branch block (LBBB) who developed complete heart block (CHB) Over a short time period conduction improved from complete block to intermittent block with a progressively shortening HV interval to persistent conduction with the HV interval again at the pre complete heart block value This case supports the concept that impaired conduction velocity through the bundle branch system can occur without complete block and is manifested by a prolonged HV interval

Case history and methods

A 5?-year-old white man was admitted to the Bronx Veterans Administration Hospital for extirpation of a melanoma on his back His past medical history was unremarkable he had never experienced episodes of dizziness or syncope and was not taking any cardiotonic medications All findings on physical examination were entirely within normal limits except for the melanoma on his back. Because his ECG (Fig. 1) showed an LBBB and an axis of −30 degrees in the frontal plane (LAD) HBE was done using a modification of the technique previously described by Damato and co-workers Records were obtained on an Electronics for Medicine recorder using a paper speed of 100 mm per second

Electrophysiologic studies. During the initial part of the study (Fig 2 upper panel) the sinus cycle length was 750 msec (80 beats per minute) and A V conduction occurred with an AH of 90 msec and an HV of 55 msec (both within normal limits) The response to atrial pacing (Fig 2, lower panels) was normal, with progressive lengthening of the AH interval from 150 msec at a rate of 100 per minute to 190 msec at 160 per minute the HV interval remained constant at 55 msec

While the catheter was being manipulated the patient went into complete heart block with the site of block found to be distal to the site of recording of the His bundle spike (Figs 3 and 4) Right ventricular pacing was immediately undertaken at a rate of 75 per minute Over the next 20 minutes when the pacemaker was transiently turned off intermittent 1 1 conduction at several HV intervals was documented Starting with an HV of 120 msec, steplike shortenings of the HV interval occurred while the AH remained unchanged (Fig 5) Persistent 1 1 conduction with an HV of 55 msec was subsequently restored

From the Cardiology Section of the Bronx Veterans Administration Hospital and Mount Sinai School of Medicine New York

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Reprint requests to Dr Rafael Levites, Assistant Director Heart Station, Division of Cardiology Hahnemann Medical College and Hospital, 230 N Broad St Philadelphia Pa 19102

*Present address Dr Jacob I Haft Chief Cardiology Section Veterans Administration Hospital 130 W Kingsbridge Rd Bronx N Y 10468.

related to duration of ingestion, consistent with a cumulative toxic effect of ethanol

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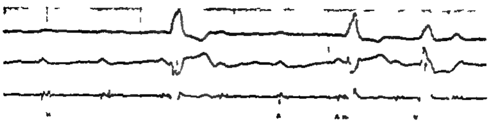

Fig 3 Complete heart block Note that each P wave is followed by a His bundle spike The first and second QRS complexes are probably idioventricular or originate in the right bundle branch or low in the His bundle and are not felt to be conducted from the atrium because of the markedly short HV interval. The third QRS may have been conducted from the atrium with a prolonged HV of 170 msec

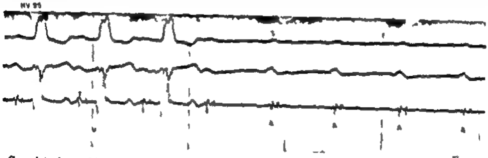

Fig 4 Complete heart block (below the His) appears after three supraventricular beats conducted with a prolonged HV Value in milliseconds

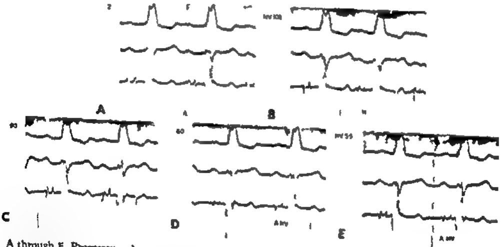

Fig 5 A through E Progressive shortening of the HV interval is shown indicating improvement in conduction down the right bundle branch AH remained constant Values in milliseconds.

normal HV documented in the initial part of the study indicated that conduction down the right bundle branch probably was normal The subsequent complete heart block and HV prolongation were due to delay down the right bundle branch probably related to trauma to the right bundle branch while the catheter was manipulated

Following complete heart block periods of intact A V conduction were documented with HV intervals that progressively shortened over a brief time period suggesting gradual improvement in the conduction through the right bundle branch. After approximately 20 minutes stable 1 1 conduction was re-established and the original

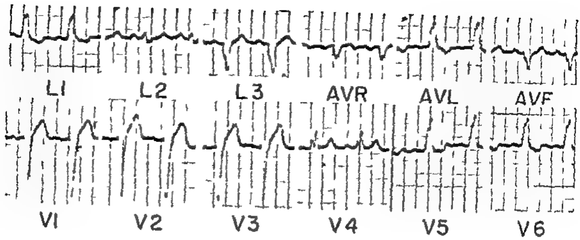

Fig 1 ECG showing left bundle branch block (mean QRS axis −30)

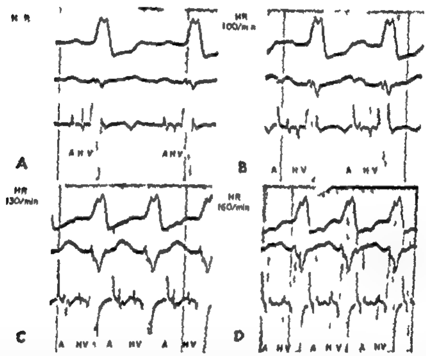

Fig 2 A through D A HBE showing normal conduction intervals during the initial part of the study (AH 90 msec HV 55 msec) *Panels B C and D* A normal response to atrial pacing was seen with the AH interval prolonging to 190 msec as the atrial rate was increased to 160 per minute The HV interval remained constant at 55 msec

Discussion

Hay[16] and Wenckebach[17] originally described what is known today as Mobitz Type I and II blocks the former was explained as due to impaired atrioventricular conduction and the latter as caused by depressed ventricular excitation With the advent of HBE a more precise study of these conduction disturbances has been made possible In general Mobitz Type I has been characterized by gradual prolongation of the AH interval while HV remains constant[1] Mobitz Type II, on the other hand presents as an intermittent block below the His bundle with the AH and HV intervals remaining constant during the conducted beats[1, 4] Based partially on this latter finding it has been suggested that conduction through the IVS acts as an all or none phenomenon[1, 4] Recently however Wenckebach periods have been documented by HBE studies[1, 3, 4, 5] to occasionally occur in the bundle branches, either spontaneously or induced by atrial pacing or atropine administration The present case further demonstrates that the IVS is capable of varying rates of conduction

Instances of CHB complicating HBE in patients with LBBB have been described[1] These patients however, frequently had prolonged HV s prior to development of CHB In this case the

Development of mitral insufficiency following closure of ostium secundum atrial septal defect

Jermiahou Ben Zvi, M.D.
Frank J. Hildner, M.D.
Philip Samet, M.D.
Miami Beach and Coral Gables, Fla.

Atrial septal defect (ASD) is the most common congenital heart disease in adults.[1] It was the first intracardiac lesion to be repaired successfully under direct vision. Surgical repair of the ostium secundum atrial defect is usually associated with low mortality and excellent results. The most frequent postoperative complications include dysrhythmias, residual shunts, and thromboembolism.[1-3] We have, however, encountered four patients who developed severe mitral regurgitation after successful closure of ostium secundum ASD's. This association is very uncommon and, to the best of our knowledge, has not been previously reported.

Case reports

Case No. 1. J. F. is a 40-year-old white female in whom a heart murmur was detected soon after birth. She was asymptomatic until the age of 24 when she began experiencing palpitations. She was admitted to another hospital where an ostium secundum ASD was diagnosed clinically and proved by cardiac catheterization (1957). She was operated in 1958 and a 4 by [illegible] cm. high and posterior interatrial septal defect was found. No mitral regurgitation was noted during surgery. The ASD was closed by a simple running suture. Following surgery, the patient was digitalized and given quinidine because of repeated paroxysmal atrial fibrillation and atrial flutter. In 1960, cardiac catheterization was repeated and revealed normal heart pressures and no evidence of a left-to-right shunt. The patient remained asymptomatic until 1967. At that time she again experienced severe palpitations and was found to have atrial fibrillation with a rapid ventricular response. Examination revealed bilateral basilar râles despite digitalis and diuretic therapy. A grade III/VI holosystolic murmur was heard for the first time at the apex radiating to the axilla. No diastolic murmurs were audible. Cardiac catheterization (Feb., 1967) revealed normal right heart pressures, a pulmonary wedge pressure of 16 mm. Hg, a left atrial pressure of 14 mm. Hg, and LVEDP of 13 mm. Hg; cardiac index was 2.97 L. per minute per square meter. Left ventricular cineangiography showed severe mitral regurgitation (Fig. 1). On March 22, 196[illegible], the patient underwent cardiac surgery. The mitral valve was found to be insufficient with marked loss of leaflet substance and the chordae tendineae were markedly shortened. The wall of the left ventricle beneath the mitral valve was fibrotic with a white abnormal appearance. After excision of the mitral valve, a Starr-Edwards prosthesis was inserted. Pathologic examination of the excised mitral valve showed deformed mitral valvulitis with fibrosis and calcification. A myocardial biopsy of the abnormal area below the mitral valve showed subendocardial fibroelastosis. Following surgery, the patient was maintained on coumadin and digoxin and remained in chronic atrial fibrillation. Catheterization in November, 1967 showed normal right heart pressures, a pulmonary wedge pressure of 10 mm. Hg, left atrial pressure of 8 mm. Hg, and LVEDP of 4 mm. Hg; cardiac index was 3.02 L. per minute per square meter. No shunts were detected. Left ventriculogram showed good contractility and a normal functioning mitral valve prosthesis without any regurgitation. Since then the patient has done well.

Case No. 2. J. H., a 3[illegible]-year-old black male, was asymptomatic until 1962 when he experienced exertional dyspnea, easy fatigability, and paroxysmal nocturnal dyspnea. He was treated with digitalis and diuretics. Examination revealed a normal sized heart with an accentuated P[illegible] which was also palpable. The second heart sound showed wide fixed splitting. A rough grade II/VI ejection systolic murmur was heard at the pulmonic area. The electrocardiogram (ECG) demonstrated normal sinus rhythm and incomplete right bundle branch block with minor nonspecific ST-T wave changes. In 1963, cardiac catheterization demonstrated normal right heart pressures with an interatrial septal defect and a large left-to-right shunt. In October, 1963, closure of a 4 by 4 cm. ostium secundum type ASD was accomplished. Upon inspection during operation there was no evidence of mitral insufficiency or cleft of the mitral valve. The ASD was repaired by suture. Following surgery the patient did very well until June, 1965, when exertional dyspnea and paroxysmal nocturnal dyspnea recurred. In November, 1965, physical examination revealed hepatic enlargement to 2 cm. below the costal

From the Division of Cardiology, Department of Internal Medicine, Mount Sinai Medical Center, Miami Beach, and The University of Miami School of Medicine, Coral Gables.

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Reprint requests to: J. Ben Zvi, M.D., Mount Sinai Medical Center, 4300 Alton Rd., Miami Beach, Fla. 33140.

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intraventricular conduction velocity (HV interval) returned This sequence of events can be interpreted to suggest that conduction within parts of the IVS system is not all or none, but can be impaired to varying degrees

Summary

Complete heart block developed during HBE studies in a patient with left bundle branch block, after inadvertent catheter induced trauma to the right bundle branch Normal intraventricular conduction (HV interval) was documented during the initial part of the study and was demonstrated to be markedly prolonged after the appearance of heart block Conduction through the right bundle branch improved over a short period of time, as manifested by steplike shortenings of the HV interval, until the original conduction velocity was re established This case strongly supports the concept that the His Purkinje system is capable of varying its conduction velocity and further demonstrates that, in patients with bundle branch block a prolonged HV interval indicates disease of the remaining bundle branch

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ECG showed sinus rhythm with complete right bundle branch block Cardiac catheterization in March 1973 revealed minimal pulmonary hypertension (31/15) Passage of the catheter from the right atrium to the left atrium and to the pulmonary vein demonstrated an ostium secundum type ASD Dye curves and oxygen samples demonstrated a very large left to right shunt Left ventricular angiogram showed a normal sized left ventricle with excellent contractions without mitral regurgitation On March 23 1973 the patient underwent cardiac surgery in which an ostium secundum ASD was found No mitral regurgitation was seen during surgery and upon inspection the mitral valve was normal The ASD was closed with continuous sutures Following surgery the patient exhibited marked symptomatic improvement and in May 1973 she had improved to functional Class II However examination during this visit revealed a new grade III/VI holosystolic murmur at the apex radiating to the axilla and suggesting mitral regurgitation In June the patient developed overt congestive heart failure in spite of treatment with digitalis and diuretics On July 3 1973 the patient had repeat cardiac catheterization which demonstrated normal right heart pressures No shunt could be detected Left ventriculography revealed severe mitral regurgitation into a large left atrium (Fig 2)

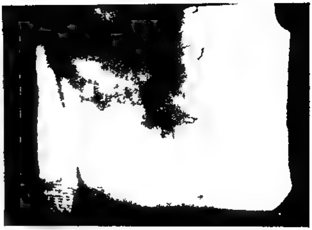

Fig 2 Left ventriculogram of R [redacted] reveals severe mitral regurgitation

Discussion

Unlike the ostium primum ASD the ostium secundum type is rarely associated with mitral insufficiency Mitral insufficiency together with ostium secundum defect is reported as being due to rheumatic valvulitis congenital mitral valve disease and undertermined etiologies[4]

All four patients reported here had ostium secundum ASD s without any mitral regurgitation initially Mitral regurgitation was not found either during initial cardiac catheterization or during cardiac surgery All four patients improved clinically following closure of the ASD However the development of mitral insufficiency caused subsequent clinical deterioration In the first patient mitral insufficiency developed nine years after the repair of the ASD In the second patient mitral regurgitation appeared two years after the ASD closure In the third patient mitral regurgitation appeared three and a half years after surgery and in the fourth patient the valvular lesion developed two months following the ASD repair In all four patients the ASD repair was successful and no residual shunt could be detected in the postoperative studies

It is impossible to incriminate a single cause or etiology of mitral regurgitation in these patients The absence of mitral regurgitation in the first catheterization when ASD was diagnosed as well as during surgery excludes congenital mitral insufficiency The interval of nine years between closure of the ASD and the development of severe mitral insufficiency in the first patient and three and a half years in the third patient excludes cardiac surgical intervention as a possible direct cause of mitral incompetence In the first patient the pathologic changes of the excised mitral valve and chordae tendineae suggested rheumatic valvulitis as the etiology of the acquired mitral insufficiency It is more difficult to assume the etiology of mitral regurgitation in the second and third patients In the second patient mitral insufficiency appeared two years following successful closure of the ASD and in the third patient three and a half years following surgery There is no clue as to the cause of this new lesion Both of these patients did not have ischemic heart disease which might have caused mitral regurgitation due to papillary muscle dysfunction Neither of these patients had any history to suggest subacute bacterial endocarditis as the pathogenic mechanism The mitral valve did not show a prolapsed leaflet in any of these patients The development of mitral insufficiency two months following ASD repair in the fourth patient raises the suspicion of mitral regurgitation being a possible but unrelated result of cardiac surgery Silent coronary embolism as a complication of ASD repair might have caused papillary muscle dysfunction with mitral insufficiency but there has been no evidence to substantiate this possibility Transient circulatory insult of the mitral valve apparatus during surgery might lead to this complication in theory All four patients developed severe mitral insufficiency accompanied by the appearance of the characteristic apical holosystolic

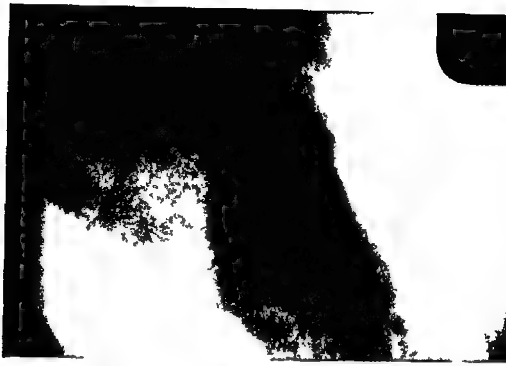

Fig 1 Left ventriculogram of J F demonstrating severe mitral regurgitation

margin On cardiac examination the point of maximum impulse was felt in the fifth intercostal space well outside the midclavicular line S was widely split and varied only a little with respiration and the second component was louder than the first component A grade III/VI holosystolic murmur was heard at the apex with radiation toward the axilla and the left sternal border A grade I/VI ejection systolic murmur was heard over the pulmonic area Cardiac catheterization showed elevated right heart pressures The right ventricular pressure was 52/16 mm Hg pulmonary artery pressure was 52/36 with a mean of 40 mm Hg A left atrial pressure of 60 mm Hg was obtained by a transseptal approach There was no gradient across the mitral valve Left ventricular cineangiography revealed a severe degree of mitral regurgitation into an enlarged left atrium No shunts were found The patient died while waiting for surgery

Case No 3 S F is a 64 year old white woman with a history of a heart murmur which was detected at the age of 18 months During childhood she was limited in her physical activities but was essentially asymptomatic until 1947 when she experienced exertional dyspnea and was digitalized In 1965 the dyspnea increased She also complained of chest pain and palpitations In 1966 the blood pressure was 125/75 mm Hg The pulse was regular at 80 per minute There were no signs of heart failure The point of maximum impulse was in the fifth intercostal space [illegible] cm outside the midclavicular line A right ventricular heave was present The first heart sound was split and the second heart sound showed fixed splitting with the first component louder than the second component A grade III/VI ejection systolic murmur was heard maximally at the pulmonic area transmitted to the aortic area and to the left sternal border The murmur was not transmitted to the neck or apex No diastolic murmurs or gallop sounds were audible ECG showed regular sinus rhythm with incomplete right bundle branch block Cardiac fluoroscopy revealed a large pulmonary artery with increased pulmonary vasculature extending to the periphery There was definite hilar dance and the right ventricle appeared to be enlarged Cardiac catheterization in 1966 revealed normal right heart pressures no valvular gradients and no mitral regurgitation An ostium secundum interatrial defect was demonstrated by catheter passage dye dilution curves and angiocardiography A large left to right shunt was documented On Nov 21 1966 the patient underwent cardiac surgery utilizing cardiopulmonary bypass An ostium secundum ASD of 2 by 4 cm was found and was closed with two continuous sutures Following surgery the patient s effort tolerance improved remarkably therefore digitalis was discontinued Cardiac catheterization on May 19 1967 revealed normal right heart pressures with no evidence of a left to right shunt In May 1970 she was seen again and except for recent onset of chest pain she was asymptomatic However examination revealed a new grade III/VI holosystolic murmur at the apex radiating to the left sternal border and axilla This murmur was typical of mitral insufficiency Catheterization at that time showed normal right heart pressures without valvular gradients or shunts The left ventricle was of normal size with slightly reduced contractility but moderate mitral regurgitation was demonstrated

Case No 4 R G is a 39 year old white woman who experienced onset of palpitations and exertional dyspnea at the age of 14 A heart murmur was detected at that time In February 1973 (at the age of 39) palpitations became more frequent and shortness of breath followed mild effort She also experienced attacks of paroxysmal nocturnal dyspnea There is no history of rheumatic fever Examination revealed a regular pulse at 80 per minute Blood pressure was 130/70 mm Hg The point of maximal impulse was in the fifth intercostal space 2 cm lateral to the midclavicular line A right ventricular heave as well as P were palpable There was wide fixed splitting of S at the pulmonic area A grade II/VI ejection systolic murmur was heard at the lower left sternal border radiating to the apex and base No diastolic murmurs were audible The rest of the physical examination was normal

Risk factors and coronary heart disease—facts or fancy?

Lars Werkö
Göteborg Sweden

Coronary heart disease (CHD) has attracted a marked and continuous interest during the last decades although the clinical syndromes classified under this general heading must be considered to be poorly defined in relation to the underlying cardiac pathology Sudden death myocardial infarction anginal pain heart failure and various arrhythmias that occur in conjunction with varying amounts of pathologic changes in the coronary arteries and with varying extent of myocardial involvement do not show any exact relation to the extent of these lesions The relation between the changes in the myocardium—fibrosis or necrosis—and the arterial process is furthermore unclear and has been the subject of different interpretations [3, 4, 32, 1, 22, 6, 55, 5, 1] Even the exact nature of the disease process that afflicts the coronary arteries in patients diagnosed as suffering from coronary heart disease is not fully understood [1, 8, 1, 22, 9, 10] Various theories have been suggested as an explanation for the arterial disease that leads to the obstruction of the coronary arteries but none have met unequivocal approval [8, 7, 7]

Several thorough studies in pathology have aimed at a better definition of the evolution of arterial disease and its consequences for the myocardium [4] The difficulties that the pathologists encounter when studying human material are however numerous No study has been done where both the total clinical picture leading to the fatal event and the morbid anatomic findings at autopsy have been analyzed with the same detailed methodology combined with a critical mind No doubt the task for the pathologist is not very rewarding as he has to try to explain the background and evolution of successive changes occurring over many years or even decades from the end result seen at the autopsy table after the final catastrophe leading to death

This lack of factual information has not discouraged bold epidemiologists or clinicians to carry out local population surveys or world wide comparative studies regarding different environmental factors supposed to be of importance for the clinical manifestations of CHD or death [8, 17, 2, 25, 35, 31, 3, 5, 1, 7, 37] In such studies the relation between such factors and death or clinical CHD has been the target for investigation Excellent correlations have been demonstrated between for example a numerical value of serum cholesterol determined once and the prevalence or incidence of CHD [37] To what extent this is due to selection of the variables for study or the countries for comparison of findings in the population is not discussed It is also seldom recorded that the populations studied are small or that comparisons are made using data of doubtful validity such as official mortality statistics or consumption figures for a whole nation One country where the population seems to behave differently regarding many of these relations is Sweden This has sometimes been noted by workers in this field but the implications are never fully discussed [3, 49]

In spite of these uncertainties the constant and repeated publication of information regarding findings that demonstrate that raised blood pressure certain smoking habits or high serum cholesterol values are statistically related to the later development of the clinical manifestations of CHD or death indicates for the medical and lay public that the problem of the present so called

From the University of Göteborg Department of Medicine WHO Collaborating Centre for Research and Training in Community Control of Cardiovascular Diseases Sahlgrenska Sjukhuset Göteborg Sweden

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Reprint requests Dr L Werkö Department of Medicine University of Göteborg, Sahlgrenska Sjukhuset Göteborg, S-413 [illegible] Sweden.

murmur Replacement of the incompetent mitral valve with a prosthetic valve was followed by marked clinical improvement in the first patient The fourth patient might also benefit from a similar approach

These patients demonstrate that clinical deterioration after successful repair of an ostium secundum ASD might be, in certain cases due to development of mitral insufficiency

Summary

The development of severe mitral insufficiency after a successful closure of an ostium secundum ASD was encountered in four adult patients This acquired postoperative lesion appeared nine years three and a half years, two years, and two months following ASD repair It was associated with deterioration of the excellent clinical improvement following closure of ASD, and was detected clinically by the appearance of a new apical holosystolic murmur In one patient, pathologic examination of the mitral valve indicates insufficiency to be possibly due to rheumatic valvulitis The cause of mitral insufficiency in the other patients is not clear Multiple etiologies could be responsible for this unusual association

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sample respondents and 307 volunteer subjects were found free of CHD on initial examination that is in all 2 283 men usually referred to as being between 30 and 62 years of age (though five men were 29 years of age)

Thus this is the group that represents the basis for all statements about factors of importance for the development of coronary heart disease other cardiovascular diseases and complications that have appeared from the Framingham study organization

Age distribution Another difficulty in judging the results from the Framingham study is the wide age range of those subjects finally taking part This has led to calculating risks for age groups of several decades something which must be especially difficult when it comes to such disorders as various clinical manifestations of cardiovascular disease with a marked age dependence The same age dependence is also true regarding the distribution of many of the risk factors studied The habit of mathematically correcting for this wide age span must be dangerous difficult and sometimes erroneous especially as chronologic age and its relation to the distribution of disease manifestations or chemical or physiologic variables has not been established in a large population sample

The follow up studies have focused on the presence of cardiovascular disease or its sequelae such as myocardial infarction sudden cardiac death anginal pain congestive failure and intermittent claudication Through good cooperation with hospitals and physicians in the area the possibility for follow up of those subjects developing any of these clinical manifestations has always been excellent while the follow up of those subjects without symptoms must have been less easy

The loss to follow up in this study is usually not reported except in the official reports going to the central offices in Washington D C Thus it is difficult to grasp the size of this error It seems probable however that it is of minor importance especially in comparison to the initial loss of the selected population Most biannual follow up studies however contain only around 70 per cent which is compensated for because different people show up at successive examinations making overall participation higher

Presentation of results Another difficulty in obtaining a clear picture of the results of this study is that they usually have been presented in a different mode for each follow up period This is especially evident when the cut off points for different risk factors and the definition of age groups analyzed are followed through the years This makes it impossible for those outside the study to compare the published results from one time period to another It is also impossible to compare the conclusions reached with those arrived at in other studies This may be one of the reasons why the many articles describing results from Framingham make no attempt to review other evidence from other epidemiologic studies and put the Framingham study into proper perspective

Comments How representative is this sample of the American men? How is the relation between this sample the Framingham male population and United States males as a group? What are the sound facts and are there bias and subjective interpretations that cannot be substantiated when a closer look is taken at the results of the Study?

Early in the study it was clear that the sample could not be considered to represent the American male population As Dawber and co workers[1] stated In fact unless the cooperation of the population is essentially complete it is difficult if not impossible to consider it a random sample as representative of a larger population It has also been indicated that the distribution of blood pressure and serum cholesterol in the population studied in Framingham differs from what has been reported from United States white males It must also be obvious that the participating families in Framingham do not reflect the wide socioeconomic range of the American community As far as can be understood from the reports neither the higher nor the lower socioeconomic strata have been represented This is however a fault common to most if not all population studies

When the population sample was originally drawn it was decided not to select individuals but families that were invited to take part in the study This in itself decreases the real number of independent participants because of a possible aggregation of some disorders physical or psychic characteristics and habits that have a familial background

It is also obvious that the loss of almost one third of the originally selected population invali

epidemic of CHD in the Western World is almost solved Certain ways of prevention and early treatment of supposed causative or premorbid states are then also thought to be at hand Some physicians and official organizations even want to implement such methods of prevention without awaiting more scientific results[36,37,43,51,54,67] while others are more cautious[6,39,41,45,50,57,63]

The lack of information about the clinical course of the presymptomatic phase and of the exact pathologic relations of the common state designed as CHD has led the World Health Organization (WHO) to inspire studies in various countries in Europe Some of these aim at better information about the incidence of myocardial infarction and sudden death in defined populations This should, at the same time, allow better structured studies regarding the circumstances around the acute phase of clinical illness

This is the more necessary, because even the best published epidemiologic studies have drawbacks that make many of the conclusions drawn questionable or at least not very well founded

The present review will attempt to analyze some details in a few well known and repeatedly published studies with the aim to establish the background against which the conclusions are drawn and thus evaluate their validity The main reason for this analysis ■ the preliminary results of an ongoing multifactorial preventive study in Goteborg The experiences gained have more than other information, demonstrated that large scale population studies constitute an immensely difficult field Lack of strict definition of terms used and of cooperation from the population studied as well as loss to follow up constitute some hazards Lack of strict definition of the clinical features and the exact cause of death constitute other hazards

As ■ basis for the following analysis, two American and one Swedish study have been used, i e , The Framingham Study The National Pooling Project, and the Stockholm Prospective Study The general design, and in particular the selection of the material for study, the completeness of the first screening investigation and follow up will be especially analyzed as well as criteria for diagnosis and some other factors studied This is of importance as these details usually do not appear in any of the many articles reporting the long term results

Framingham study The Framingham study[14,18,21,23,25,34,61] started in 1948, with ■ selection of the population in the city of Framingham Mass and has been conducted as a thorough biannual follow up, the results of which have been published during the last few years

Selection of material for study Originally, 6 510 individuals in Framingham between the ages of 30 and 59 (as of Jan 1, 1950) and of either sex were invited to take part[11] Of these, less than 70 per cent answered the invitation Because of this 734 healthy volunteer subjects were added to the original sample later The total base population studied thus consisted of 2 283 men and 2 844 women, all between the ages of 30 and 62 years

The first examination lasted for four years[11,14] which led to the extension of the studied age span up to 62 years Even though this happened five men and nine women were only 29 years of age at the origin (When the first report was published)

Because of the findings of pre existing cardiovascular disease 53 men and 29 women were excluded from the study Those with questionable symptoms or signs of disease—which were not defined—were included As one of the aims was to analyze the importance of certain risk factors, patients with arterial hypertension were included, but no treatment was administered through the study group The participants personal physicians were however, notified of the findings at the first investigation and were free to administer any type of treatment that they saw fit The same holds true for hyperlipidemia which, at the start of the study, was registered as high blood cholesterol

As the male morbidity and mortality are of greatest interest and this has been the most important aim for Framingham Study the following discussion will be focused on the study of the male part of the population

Originally 3 086 men aged 30 to 59 were asked to take part in the study Of these, only 2 036 persons responded (66 per cent) with higher percentage in the investigation being in the younger age group and the lowest percentage being in the higher age group (58 4 per cent) It should be noted that each final five year age group consisted of between 261 and 417 men with a clear age gradient In order to increase the number of participants in the study a group of volunteer subjects was finally added to the sample (312 men) Of these participants 1,976

possible individual bias methodologic variations and varying observer errors may have introduced errors which are all hidden by the smoothing procedure of mathematical transformation of the mass of data into one seemingly homogenous series of observations The above criticism against the Framingham study thus cannot be less regarding the primary data of the NPP It seems rather probable that more criticism can be raised regarding this part of the project even though no comments about selection have been published so far

To transfer the data mathematically to the whole United States male population cannot be sound when the selection difficulties are considered

Presentation of the results Two main comments have to be made regarding the presentation of data One is about the purely numerical presentation of the pooled material the other is about the conclusions drawn regarding the importance of different risk factors

The same figures or illustrations are used in the several publications about the NPP For sake of simplicity the following comments are referring to the data presented in the report of the Intersociety Commission [6]

NUMBERS OF INDIVIDUALS FOR STUDY This number varies between 7 312 and 7 594 subjects in different tables and figures Which of these basal values the authors use for calculation of different rates is impossible to know There is no mention in the text why these numbers vary which makes the reader uneasy about the quality of the whole study

The main interest is focused on the conclusions based on rates of new events (after many mathematical maneuvers) It is also commendable that the number of events are given in the different relations illustrated though no comments about definition of the events are made It is then rather perplexing to find that the number of a specific event for example any major coronary event varies not only between figures presented but also within the same figure (in different panels) Even worse is that differences between the number of the same event in two panels in one figure may be larger than differences of the total population in the same panels This is the case in Fig 10 where the upper part gives figures for 7 427 men who experienced 589 events and the lower part for 7 342 men with 479 events This means that there were 110 more events for 85 more men? There is no obvious explanation for such differences that come to mind and it is rather sad that no comment is found about this in any of the publications that have appeared so far

GENERAL COMMENTS AND CONCLUSIONS There are two reasons why it is important to concentrate the discussion on the reported death rate especially sudden death One is that both sudden and total cardiovascular death are events that cannot be disputed in contrast to major events which is poorly defined The other is that the rationale for defining risk factors of importance for developing CHD is an attempt to define preventive measures for the large number of patients that die before reaching medical care

The general tenor of the NPP reports as of most others is the emphasis on three specific risk factors—raised blood pressure, high serum cholesterol, and cigarette smoking Of these high serum cholesterol—and its presupposed dependence on the American diet—is given main emphasis also in correspondence with most other reports in this field

Regardless of the lack of proof that it is the American diet that causes an elevation of serum cholesterol in the population samples studied the discussion focuses on the necessity of changing the diet of the general population It seems therefore rather remarkable when looking at the results regarding deaths—that there is not any straight line relation between the level of serum cholesterol and the incidence of these deaths This is in clear contrast to both blood pressure and cigarette smoking where this relation is clearly related to elevation or amount of smoking in a rectilinear fashion

This way of analyzing each risk factor by itself is however questionable as a large number of individuals in the population are characterized by having more than one risk factor The number of individuals characterized by one or more risk factors are dependent on where the cut off point for each risk factor is placed With the definitions used in this presentation of the NPP data the number of individuals at highest risk (three risk factors) is 595 while 1 249 men exhibited no risk factor at all

With coronary heart disease having a multifactorial background, the relation of all new clinical events and sudden death all cardiovascular

dates the representative aspects of the study The addition of volunteer subjects' to the sample studied does not improve the situation Rather it must decrease the value of the results arrived at, in particular when it comes to referring to the general American male population

That the volunteer subjects do not represent the same base population as the other subjects is also shown at one of the earlier follow up periods when the six year incidence of new CHD was 8 out of 52 in the volunteer subjects as compared to 19 out of 301 of the random sample (age group 50 to 54 males) [16]

When the Framingham study was designed,[11 16] much thought was given to its objectives Much consideration was given the difficulties inherent in a population study and the necessity of formulating hypotheses to be tested A number of specific questions were thus formulated which ought to be answered These questions involved the relationship of age sex, family history, occupation, educational level national origin serum lipid levels, and physical activity (among others) to the development of CHD [15] Due to the large numbers of nonrespondents, many of these questions have later been dropped Other more clinically oriented questions have been added during recent years

The most valuable information published as a result of the Framingham study bears on the relationship of serum cholesterol levels, blood pressure and habit of cigarette smoking to the future development of clinical cardiovascular disease, with the reservations necessary due to the wide age span of the population and the possible over representation of certain family traits

In this connection a note of caution is particularly important in respect to hypotheses which were not postulated prior to the study, but are derived from the data generated by the study

We have found that the mortality from cardiovascular disease and other usually not well defined causes for death is several times higher in a Swedish city population among those not answering to an invitation for health examination than in those coming to the investigation (which may be seen as an indication of their interest in health problems) This was found although the rate of adherence was 75 per cent and thus the loss only 25 per cent as compared to the more than 30 per cent loss in the Framingham study Similar results have also been published from Framingham when they were recording the death rate of the nonrespondent group

The subjects of the study who were born in 1913[66] also demonstrated that there was an important difference between those not taking part and those interested in the study, even though close to 90 per cent of the randomly selected population was investigated

British experience in multiphasic health screening also indicates a difference in morbidity and mortality between respondents and nonrespondents

These considerations regarding the mode of selection of the populations for the Framingham Study thus lead to the conclusion that any result of this study is only applicable to that part of the population of the city of Framingham that has taken part in the study, i e , at best a middle class suburban population in a fairly good economic social, and educational situation

Instead research workers of all kinds have used the Framingham data as if it represented the male population not only in the USA, but in the whole Western industrialized part of the world

National Pooling Project (NPP) [31 62 66] In an attempt to arrive at conclusions that were based on a large population series several American prospective studies have agreed to pool their data obtained in the male part of the population studied Thus, NPP was created through collaboration between Framingham Albany Chicago and Western collaborative studies, comprising about 7,000 men The most recent analysis is presented as the 10 year incidence rate of CHD found in these investigations recalculated to correspond to the age structure of the American male population A preliminary analysis from this large collaborative effort occupies most of the several reviews published in the United States during the last two years, which makes it imperative to discuss the results and conclusions

Selection of population It is impossible from the presented material to elucidate how the basal population was selected The relations in number and age groups between the various base studies in the final presentation are also not reported It may, however, suffice to state that this pooling of data can never counteract possible flaws due to original selection difficulties On the contrary, even though it may seem of great help to add experiences from several centers the inequality in sampling procedures varying incidence of disease

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comparatively few men is not mentioned or even discussed

Also here the base population was characterized by a rather wide age range The different numbers mentioned in the different papers referring to the basic male population for study makes it impossible to know the age distribution of the sample The authors only divide the participants into two groups below and above 40 years It seems certain however that the age span is large as it was between 20 and 70 years of age in the original study

The number of events are fairly small which may be due to a large number of young males in the population the lack of direct investigation at follow up and too rigid an exclusion criterion

The factual results of the SPS that are subjected to rather complex but not very sophisticated mathematical analysis are thus based on a study where the base population is unknown definitions both at the outset and later are unclear and where exclusions both at the outset and at follow up are made on uncertain and haphazard grounds Bot the initial design the way of follow up and the lack of any firm criteria for diagnosis of the disorders that are the target for study make the results of the SPS unreliable The results of studies conducted like this one should not be allowed to confuse the issue for those trying to get a clear picture of the present situation regarding the importance of the risk factors for CHD by perusal of the literature

It is therefore remarkable and a little sad that many investigators editorial boards and editors accept the wide sweeping general conclusions made in a study using such inexact criteria

General comments Epidemiologic studies are necessary in order to increase our knowledge about the pattern of disease found in the population They should also lead to the formulation of hypotheses about etiology and pathogenesis especially as regards the influence of environmental factors in the hope that they may be possible to influence These hypotheses should before they are accepted be tested using other more experimental methods Most epidemiologic studies are usually only descriptive but might be designed more as an experiment for example through some kind of intervention

In order to formulate well founded hypotheses it is important that certain basic rules are adhered to when studies of the epidemiology of a disorder are designed and conducted If conclusions are made regarding larger or other populations than the one studied there must be some guarantee that the selection of the population to be studied as well as the study are unbiased and that enough of those selected as participants also take part in the study It is also important at the outset to have well defined objects for study regarding the selected population (age and sex) and physiologic measurements (serum cholesterol body weight and blood pressure) It is equally important to have rigid criteria for diagnosis of the disease studied both at the start and at the end of the study

The importance of finding leads to construct hypotheses about the pathogenesis of coronary heart disease have encouraged many epidemiologic studies Most of them have either studied only males—in the community, or employed in one or more companies—or concentrated the discussions of the results on the male part of the population studied Now when several of these studies have reached a stage where it may seem possible to arrive at rather far reaching conclusions—as some have already done—the time has also come to scrutinize the initial design and conduct of the study in order to test the validity of the conclusions reached

This is of still greater importance as it is usually impossible to find any details of the initial design of the various studies in the later more or less final reports containing important conclusions of clinical relevance The tendency has been to use more and more elaborate statistical methods and less of the primary figures in consecutive publications This may then obscure some factor of importance in the original design of a particular investigation—the number and age span of cases originally taken into the study the exact mode of diagnosis of the disease processes or *causes of death* studied or the long term adherence to the original study design to mention only a few

Only if such variables are well defined at the start and adhered to during the whole course of the investigation will it be possible to extract optimal information out of the study material Using sophisticated statistical methods may then be of considerable help On the other hand if there are important weaknesses in the primary material

deaths or total number of deaths have been calculated against the number of risk factors Here a significant rectilinear correlation is demonstrated between number of risk factors and incidence of these events

However when an attempt is made to evaluate the relative importance of each of the three studied risk factors for the outcome there is again a rather curious—and not commented—result (fig 10) [1] The combination of high serum cholesterol and high blood pressure (C + H right panel fig 10) does not seem to carry an increased risk for sudden death in this American male population for 10 years as compared to those subjects without risk factors at all On the other hand the addition of smoking to either high cholesterol or high blood pressure, or both increases the risk about fourfold The addition of high cholesterol to only one of the other risk factors does not seem to increase the risk in the absence of the other factors

The only way of interpreting this is that cigarette smoking added to high cholesterol or high blood pressure, or both, is of importance while no single risk factor is of any greater importance by itself This is in good conformance with results of other better controlled studies

It seems then rather remarkable that the involved authors—and official bodies—continue to stress high serum cholesterol and diet as the risk factor that has to be controlled through general and individual intervention

The Stockholm Prospective Study (SPS) [7 8 10]
The population in this study constitutes those employees in several Stockholm industries and shops that took part in a health screening in 1961 1962 The screening was performed by several physicians employed for the purpose of checking health in those Stockholm industries that wanted their employees to have a continuous health check

Selection of population for study It is impossible to know how many were employed at the time of the first screening but altogether 8 464 individuals took part in this study Many of these 3 624 men and 2 840 women between 20 and 70 years of age were not deemed to be quite healthy The first publication from this study[10] focuses on the levels of serum cholesterol and serum triglycerides while other findings are described in a rather cursory manner or not at all

In this original publication, after rather extensive exclusions due to minor or major health defects 1,266 men and 949 women constituted the normal series The authors of this early publication state that the population to a large extent was characterized by the selection methods It constituted 77 1 per cent of those undergoing a voluntary health examination which in turn was drawn from a majority" of those working in certain industries and shops in Stockholm As stated at that time care must be exercised when conclusions are drawn as those firms taking part in this health examination had an over representation of white collar workers

Follow up procedure The first follow up was done in 1970 [7 8] and the results have been widely publicized This follow up did not constitute however, a repeated investigation of the study population A postal questionnaire was sent to all participants of the earlier study asking whether they had a myocardial infarction In case of a positive answer the hospital records were obtained and scrutinized Totally, 92 per cent answered and only those where hospital records confirmed the diagnosis were accepted as surviving myocardial infarction [8]

In those who had died in the meantime the investigators only scrutinized the death certificates and checked these against hospital records and autopsy reports Only those dying who had been subjected to autopsy were included as dying from myocardial infarction or CHD This has led to the uncommented fact that, among males 22 deaths in the series were described as other vascular deaths Most of them had however been treated for CHD and suffered an unequivocal ischemic heart disease death and would thus have been included in all other comparable studies The death certificate in these cases also registered these deaths as due to CHD The importance of this group is shown by the number (22) which is higher than those accepted as dying a sudden or unwitnessed CHD death

Comments It is impossible to find out how the original series was defined as it was now stated that 3,168 men constituted the original population In the former publication however only 1,266 men were registered in the normal series How the exclusion has been done or what constitutes the characteristics of those major disease categories that in 1970 led to the exclusion of

men They also stress the importance of separating myocardial infarction from angina pectoris as different diseases To this may be added that sudden death myocardial infarction and anginal pain may be quite different expressions of a disorder with only a partly similar background

How important then is the criticism against the conclusions of some of the epidemiologic studies? It is difficult to judge exactly to what extent the conclusions are invalidated because the base population at close scrutiny does not correspond to what the authors had intended In many cases and especially regarding some of the positive findings it may be of only minor importance In other instances especially when it comes to evaluate the importance of one factor against another or when the conclusions have been that some factor is not of importance the selection methods and large number of nonresponders may invalidate many of the general results

The Framingham study which is often quoted as the model for cardiovascular epidemiologic work certainly started out to be one This had led to the misconception that the results obtained in Framingham are true for the American people especially the white male population and as a consequence also for other white males in the Western industrialized communities When it is apparent that serum cholesterol values blood pressure overweight and smoking habits are different in the study population in comparison to the population in the community it is less certain that the results in Framingham are applicable outside the study population

This should also be a warning against using the Framingham data for all kinds of analyses of different disorders in the population

It is also clear that no information has been given about possible treatment of lipid disorders overweight or elevated blood pressure in most studies The results are quoted as if they were applicable to the untreated (or natural) state It seems reasonable that in a rather prosperous community such as Framingham on the outskirts of Greater Boston the population should have been under treatment for many of these disorders although not administered through the study group In the earlier publications it was considered to be of importance that the participants personal physician was informed about the results of each examination though he did not receive any advice about treatment If and how or to which extent such treatment influences the results is unclear

The wide age span in most studies is unfortunate as many factors change in importance with age in an unpredictable manner The statisticians may feel confident about the mathematical possibility of correcting for this I do not It does not seem possible to stratify death rates or incidence of heart attacks according to age or any other variable as long as our knowledge is so limited Many of the individuals in some of the studies especially at the younger and older end of the spectrum seem to have been used only to fill out the number of participants The use of a group of the same age has shown the feasibility of doing an epidemiologic study in males where no mathematical correction for age is required One criticism has been that this gave too small a series for study—but compare 855 men all of them 50 years old with the Framingham groups comprising 250 to 350 men in each five year group

The results of most epidemiologic studies have demonstrated the importance of high blood lipids cigarette smoking and raised blood pressure as factors indicating increased risk for sudden coronary death or the development of myocardial infarction The designation of these three cardinal risk factors for the development of coronary artery disease has emphasized the multifactorial background of the disease Nevertheless the most active epidemiologists working in this field emphasize the importance of serum cholesterol—or high blood lipids—as *the* risk factor Many want therefore to recommend far reaching dietary measures in order to control the blood lipids in the population as the most important preventive measure against CHD It is then rather surprising to find the following statement from the Framingham group in the balance blood pressure appears to be the strongest of the factors considered for coronary heart disease and atherothrombotic brain infarction For either clinical event there appears to be little difference in the strength of this factor from one age group to another "[24]

As shown here from the data of the NPP cigarette smoking added to either one of the other two risk factors or both seems to have the strongest influence on the development of cardiovascular disease or sudden death This is in good agreement with several analyses of various risk factors

no statistical treatment can correct for such flaws

Another reason for looking into the primary design of these studies is the habit of referring to many conclusions of epidemiologic studies as if they were already established facts In most instances they are only hypotheses based upon rather uncertain background material

Many review articles within this field either demonstrate the same tables and figures—at times presented in slightly different fashion—in different articles or just refer to figures from another review article without questioning the validity of the statements made This custom has already led to a too widespread acceptance of results of questionable reliability as facts agreed upon by the scientific community

The importance of defining the primary material and the disease syndromes that are selected for study became obvious when the design was contemplated and the first part of the preventive study started in Goteborg The mode of selecting the population the way of making a firm diagnosis and the importance of getting as many as possible of those randomly selected to take part in the study soon became major problems, as we wanted to get results that were both reliable and applicable to the whole city population in question

This review has analyzed some details in three well published epidemiologic studies—the Framingham study the National Pooling Project and the Stockholm Prospective Study with the aim of defining to what extent the results published are valid for the study population and relevant for any larger population One way of investigating whether the base population used for epidemiologic studies really represents the general population is to compare the mortality—both cause specific and total—with the official figures for the country, or community in question It is rather remarkable that few such comparisons have been made in all studies published In some of the earlier publications from Framingham it was found that the mortality from CHD in the investigated sample was different from the mortality in the community and also that there was a rather marked difference in cardiovascular and total mortality between the responders and non responders This latter observation conforms with our experience in Goteborg

To use the figures for total death rates published in the studies in order to compare with official figures is difficult and usually impossible Specific death rates may however, sometimes be calculated Some information bearing upon the representativeness of the studied series may then be gained by comparing the relative fractions of different causes for death in the official mortality figures with those found in the various situations studied Doing this it is usually found that the total mortality is less and the fraction occupied by cardiovascular diagnosis greater in most epidemiologic studies than comparable official figures The explanation for this may vary Most important is that this demonstrates that the base population studied does not represent a true sample of the population

The observation that the prevalence of high blood pressure or the distribution of serum cholesterol values, obesity, and smoking habits differ in some study populations from what is found in the general population similarly demonstrates that the study population constitutes a selected sample The main reason for focusing the attention on the design of some epidemiologic studies is that the important conclusions of these studies are used to reflect on measures recommended for the total population It must then be required that the studies the results of which are used as basis for these recommendations really represent the most important and prevalent risk factors as they occur in the population This does not seem to be the case

We have found that low social class social alcohol problems, low income, and lack of education are factors of importance for the later occurrence of myocardial infarction or sudden death in a Swedish city population These factors were also more common in the part of the population that did not come to the population survey or health control than in those responding Similarly both sudden death and death from all causes were more common in that part of the population sample not willing to participate than in those who appeared As the circumstances certainly are similar in the United States as in Sweden the importance of a thorough analysis of the nonparticipating group is obvious before accepting far reaching conclusions from studies of limited populations

Similarly Medalie and co workers[" "] have demonstrated the importance of several other risk factors than is conventional in a group of Israeli

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Treatment of high blood pressure and anti smoking campaigns thus emerge as more important preventive measures rather than changes in the general diet

Most epidemiologic studies have also shown a lack of importance of many other factors especially those indicating socially less fortunate individuals—as low income alcohol problems and low education That this emphasis on some and lack of importance of other factors may be due to the selection of population groups for study has not been sufficiently noticed It seems probable that the inhabitants who were willing to participate in the Framingham study—not to speak of 'volunteer subjects in that study—as well as those employed in certain industries and chain stores in Stockholm constitute a selected part of the population with less social alcohol and economic problems than the unemployed part of the population or those belonging to the lower socioeconomic strata of the community that are not interested in health problems and not willing to take part in a health examination

The results from such studies can only reflect on the factors operating in that part of the population that has been studied They should not be used for any general recommendations about interference with certain factors that, on uncertain grounds are deemed to be of importance for the total population

Summary

The importance of the many well published epidemiologic studies for the philosophy of prevention of ischemic heart disease has led to this analysis of the background design and early results of three such studies i e the Framingham study the National Pooling Project and the Stockholm Prospective Study Besides indicating certain flaws in the early design it is demonstrated that the authors usually press their factual data to conclusions that are not really valid with some exceptions This analysis leads to the conclusion that high blood pressure and cigarette smoking seem to be much more important for the development of ischemic heart disease than high serum lipids in the populations studied They are furthermore selected in such a way that the results cannot have any bearing on the general population and, in particular on its lower and higher social strata

Dr L Wilhelmsen and G Tibblin have given valuable criticism on the *manuscript*

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Total anomalous pulmonary venous connection Report of 93 autopsied cases with emphasis on diagnostic and surgical considerations

Georges Delisle M D
Masahiko Ando M D
A Louise Calder M D
J R Zuberbuhler M D
Sol Rochenmacher M D
Luis E Alday M D
O Mangini M D
Stella Van Praagh M D
Richard Van Praagh M D
Boston Mass Pittsburgh Pa Dover N.H and Cordoba Argentina

Although first described almost two centuries ago by Wilson total anomalous pulmonary venous connection (TAPVC) still constitutes a frequently difficult challenge both for the cardiologist and for the cardiovascular surgeon This study was undertaken in an effort to clarify the diagnosis and surgical management of this often rapidly lethal condition

Material

This is the largest series of TAPVC published to date to our knowledge The 93 autopsied cases came from three hospitals The Children's Hospital Medical Center Boston 91 cases* the Children's Hospital of Pittsburgh and the Wentworth Douglass Hospital of Dover one case and the Hospital Privado of Cordoba Argentina one case

From the Departments of Cardiology and Pathology Children's Hospital Medical Center and the Departments of Pediatrics and Pathology Harvard Medical School, Boston Mass from the Department of Pediatric Cardiology Children's Hospital of Pittsburgh Pittsburgh, Pa from the Department of Pediatrics Wentworth Douglass Hospital, Dover N H and from the Departments of Pediatrics and Pathology Hospital Privado Cordoba, Argentina

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Reprint requests to Richard Van Praagh M D Children's Hospital Medical Center 300 Longwood Ave Boston Mass 02115

*Fifty four of these cases have formed the basis of four prior publications from this institution but the detailed anatomy has not been presented previously

Findings

The median age at death in the 93 cases was only 7 weeks ranging from stillbirth to 19 years

There was a male predominance males/females = 1 6/1

The relative frequency of the various types[3] is presented in Table I TAPVC is classified in terms of the various sites of connection of the anomalous venous pathway[1] and of the presence or absence of other types of congenital heart disease (Tables II and III)

In each type of isolated TAPVC the presence or absence of obvious anatomic obstruction of the anomalous venous pathway is summarized in Table IV and the median ages at death in each group are given In the 30 patients with obstruction the median age at death was only 3 weeks ranging from 36 hours to 4 months In the 28 patients without obstruction the median age at death was 3 months ranging from stillbirth to 19 years

Regarding the diagnosis of obstruction of the anomalous venous pathway pressure data obtained at cardiac catheterization in 38 autopsied cases of isolated TAPVC are summarized in Table V 19 with obstruction and 19 without

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Table V Pressure data at cardiac catheterization in 38 autopsied cases of isolated TAPVC

Site of TAPVC	With obstruction						Without obstruction					
	Age at cath.	PA pressure (mm Hg)		SA pressure (mm Hg)		PA/SA	Age at cath	PA pressure (mm Hg)		SA pressure (mm. Hg)		PA/SA
Snow man	5 days	60/38	(53)	48/38	(45)	1.25	3 wk	4?/10	(?0)	86/54	(?0)	0 49
	5 days	101/53	(70)	72/51	(60)	1 4	6 wk	90/		64/45		1 4
	9 days	90/50	(6?)	60/38	(45)	1 5	3 mo	92/50	(65)	88/50	(65)	1.2
	1 mo	8?/37	(51)	6?/25	(38)	1 3	3 mo	75/40	(50)	?8/40	(45)	1.29
	6 wk.	110/55	(80)	65/40	(55)	1 68	4 mo	8?/?0	(68)	100/60	(80)	0.8?
	3 mo	74/3?	(54)	72/		1 15	4 1/? mo	80/40	(5?)	88/50	(6?)	0 91
							4 yr	23/7		84/50	(?0)	0 27
Right SVC	13 hr	75/45	(52)	75/45	(5?)	1.0	1 yr	28/12	(18)	90/52	(?0)	0 31
	3 days	86/46	(64)	62/40	(52)	1 38	7 ?/3 yr	30/10	(21)	103/?0	(50)	0.29
	7 days	94/55	(0)	77/50	(58)	1.21						
	?3 days	112/40	(70)	145/104	(120)	0 77						
	2 mo	90/30	(60)	80/		1 12						
Coronary Sinus							6 days	54/?0	(36)	78/36	(68)	0 69
							8 days	44/12	(24)	80/		0.55
							3 wk.	88/50	(63)	7?/50	(60)	1.2
							25 days	65/24	(3?)	65/		1 0
							7 wk	6. /?0	(40)	85/45	(65)	0 76
							3 mo	80/35	(50)	6?/		1.23
							10 mo	36/8	(?1)	83/5?	(68)	0 43
							1 yr	51/15	(3?)	108/84	(8?)	0 47
Ductus venosus	5 days	77/28	(35)	50/31	(43)	1.54						
	12 days	101/45	(64)	68/31		1.5						
	wk.	90/50	(70)	60/40		1.5						
	3 wk.	103/		65/50		1.58						
	3 wk.	110/58		70/40		2 0						
	mo	88/51	(68)	110/54	(84)	0 8						
Mixed	16 days	105/		100/60	(80)	1 05	20 days	38/15		?0/43	(51)	0.54
	8 wk.	90/4?		90/		1 0	7 mo	46/?5	(3?)	84/		0 5

Pressures ot simulta eous PA = pulmonary artery SA = systemic artery mean pressures are shown in parentheses.

from the dorsal atrial wall into the lung buds this vein first being identified with certainty at the 4 6 mm stage when the estimated age since ovulation was 27 days (Fig 1)[4] If supracardiac or subdiaphragmatic the anomalous venous pathway is much longer than normal The common pulmonary vein (Fig 1) short circuits the pulmonary venous return from the lungs to the left atrium and this appears to lead to the involution through disuse of the various anastomoses between the veins of the lung buds and the systemic veins

From the developmental standpoint these so called anomalous pulmonary venous connections are neither anomalous nor pulmonary These are normal embryonic anastomoses unusual in the postnatal individual but not in fact abnormal, and they clearly are not pulmonary veins the common pulmonary vein being absent The foregoing points are illustrated by two patients not included in this series in whom the pulmonary venous return to the left atrium was normal but in whom a total anomalous pulmonary venous connection also co existed to the right superior vena cava in one case (A61 68) and to the left superior vena cava and thence to the coronary sinus in the other (A63 162) No change in terminology is suggested the foregoing points being made only in the interest of understanding These postnatally anomalous pulmonary venous connections are normal embryonic anastomoses between the lungs and the systemic veins that usually involute following the development of the common pulmonary vein

The failure of the common pulmonary vein to

Table I Classification of 93 cases of TAPVC by frequency

Frequency	Site of anomalous connection	No of cases	Per cent of series
1	To left innominate vein ("snowman")	24	26
2	To ductus venosus (subdiaphragmatic)	22	[illegible]
[illegible]	To coronary sinus	17	19
4	To right superior vena cava	14	15
5	To right atrium	7	8
[illegible]	To more than one level ("mixed")	5	5
7	To azygos vein	2	2
8	To left superior vena cava	2	2
	Totals	93	100

Table II Classification of 93 cases of TAPVC by presence or absence of other congenital heart disease

	No of cases		Per cent of series	
Isolated TAPVC	58		62	
Nonisolated TAPVC	35		38	
Without heterotaxy		12		13
With heterotaxy†		23		25

Isolated TAPVC = no other congenital heart disease was present nonisolated TAPVC = other congenital heart disease co existed
†Asplenia 14 cases rudimentary spleen and polysplenia eight cases asplenia syndrome but with normally formed spleen one case

Table III Classification of 93 cases of TAPVC by site of connection and by presence or absence of other congenital heart disease

Site of connection	Isolated	Nonisolated	Totals No	Totals %
Supracardiac				
To left innominate vein ("snowman")	20	4	24	26
To right superior vena cava	6	8	14	15
To azygos vein	2	0	2	[illegible]
To left superior vena cava	0	[illegible]	2	2
Cardiac				
To coronary sinus	11	6	17	18
To right atrium	0	7	7	8
Subdiaphragmatic				
To ductus venosus	14	8	22	24
Mixed				
To more than one level	5	0	5	5
Totals	58	35	93	100

Table IV Obstruction of anomalous venous pathway in isolated TAPVC

Site of connection	Obstructed: No of cases	Obstructed: % of group	Not obstructed: No of cases	Not obstructed: % of group	Median age at death: Obstructed	Median age at death: Not obstructed
Lt Innom V ("snowman")	8	40	12	60	4 wk	14 wk
RSVC	4	67	2	33	2 wk	2 1/2 yr 9 1/3 yr
Azygos V	2	100	0	[illegible]	36 hr & 23 days*	
CoS	0	0	11	100	[illegible]	7 wk
Subdiaphragmatic	14	100	0	0	3 wk	0
Mixed	2	40	3	60	17 days & 8 wk	5 mo

*Surgical death. When there were only two cases in a group both ages at death are given rather than the median CoS = coronary sinus Lt Innom V = left innominate vein RSVC = right superior vena cava

More than a third of this series of 93 cases consists of TAPVC associated with other types of congenital heart disease i e nonisolated TAPVC (35 cases 38 per cent of the series Table II) The salient findings in this complex and fascinating group are summarized in Tables VI and VII

Discussion

In order to define the condition under discussion, we may begin by considering the question *What is TAPVC?* From the embryologic standpoint TAPVC is failure of development of the common pulmonary vein as was appreciated by Lucas and associates[6] As a consequence of this failure of development an anastomosis almost always persists and enlarges between the pulmonary venous plexus of the lung buds and the systemic veins Such anastomoses at the supracardiac (anterior cardinal), cardiac (sinus venosus), or subdiaphragmatic (omphalomesenteric) level—or at several of these levels[2,7]—normally undergo involution following the development of the common pulmonary vein Normally the common pulmonary vein appears to grow outward

Fig 1b Close up view of same embryo to show CPV (Original magnification ×250) *Atr* = primitive undivided atrium *AVC* = atrioventricular canal *BC* = bulbus cordis, future right ventricle *LL* = left lung bud *RL* = right lung bud *SV (R)* = right horn of sinus venosus *Vent* = ventricle of bulboventricular loop future left ventricle (Reproduced with permission from Van Praagh R., and Corsini, I AM HEART J 78 379 1969)

lethal disease This is perhaps best indicated by the median ages at death whole series 7 weeks isolated TAPVC with obstruction of the anomalous venous return 3 weeks and isolated TAPVC without obvious anatomic obstruction of the anomalous venous pathway 3 months In the various types of isolated TAPVC (Table IV) it is seen that obstruction of the pulmonary venous return adversely affected longevity

In the supracardiac type of isolated TAPVC the incidence of obstruction was remarkably high (Table IV) 14/28 cases 50 per cent

In the snowman type obstruction occurred at two sites behind the left pulmonary artery or at the junction with the right superior vena cava (RSVC) The commoner type of obstruction in the "snowman found in six of these eight cases occurred when the left vertical vein passed behind the left pulmonary artery instead of in front of the left pulmonary artery which is more frequent and is not associated with obstruction (Table IV) In this commoner type of obstruction with the snowman the left vertical vein passed between the left pulmonary artery anteriorly and the left bronchus posteriorly as was also found by Nakib and associates[9] The left pulmonary artery and the left bronchus together formed a vise that externally compressed the left vertical vein (Figs 3 4 and 5 *a*) In two of these six obstructed snowmen there was marked poststenotic dilatation of the left vertical vein above the level of the left pulmonary artery and the left mainstem bronchus (Figs 3 and 4) as was also observed by Kauffman and associates[1] In one of our cases (Fig 4) the dilatation of the left vertical vein could be seen as an unusual convexity of the left upper heart border in the plain posteroanterior chest x ray and following injection into the main pulmonary artery the poststenotic dilatation of the left vertical vein was clearly visualized by cineangiocardiography in the posteroanterior projection

The less common site of obstruction in the snowman type of isolated TAPVC was marked

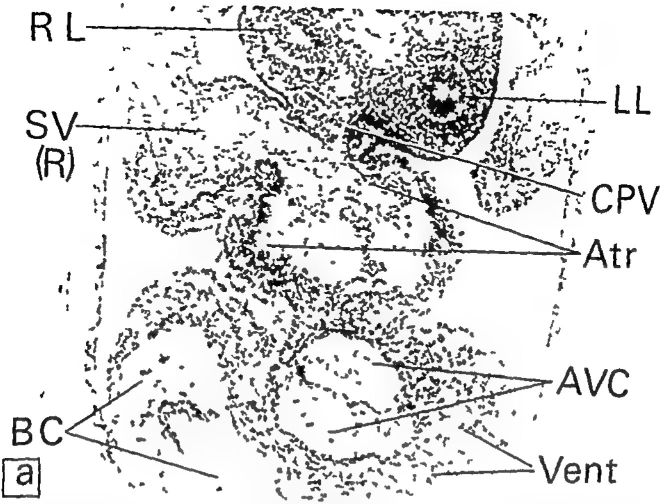


Fig 1a Development of the pulmonary vein in man horizontal plane (transverse) sections Youngest embryo in which the common pulmonary vein (CPV) was identified with certainty Harvard Embryo No 2321 4 6 mm., estimated ovulation age 27 days section 2?7 (Alum cochineal and orange G stain original magnification ×1?0)

develop in TAPVC may be due to several different processes (1) failure to appear (agenesis) (2) disappearance (involution) or (3) appearance but remaining an uncanalized cordlike strand (atresia)

In the great majority of these cases (91/93 97 per cent), no remnant whatever of the common pulmonary vein was found supporting the concepts of agenesis or involution Occasionally however a cordlike strand was found (in three of our 93 cases 3 per cent) suggesting atresia of the common pulmonary vein (Fig 2)

Parenthetically it should be added that *partial anomalous pulmonary venous connection* is merely persistence of some of the embryonic anastomoses between the pulmonary venous plexus of the lung buds and the systemic venous system The common pulmonary vein developed but may have established contact with only one of the lung buds

Total series In the series as a whole the order of frequency of the various types of TAPVC was (Table I) (1) to the left innominate vein—the familiar snowman 26 per cent, (2) subdiaphragmatic 24 per cent, (3) to the coronary sinus 18 per cent and (4) to the right superior vena cava 15 per cent There were four other types with frequencies of less than 10 per cent (Table I) TAPVC was the only type of congenital heart disease present (isolated TAPVC) in 62 per cent whereas TAPVC co existed with other types of congenital heart disease (nonisolated TAPVC) in 38 per cent (Table II)

When the whole series is classified both in terms of the site of the anomalous venous connection and in terms of the presence or absence of other types of congenital heart disease (Table III) it is of interest to note that the snowman type usually occurred as isolated TAPVC that TAPVC to the right superior vena cava was more often not isolated and that TAPVC to the right atrium co existed with other types of congenital heart disease always

Isolated TAPVC TAPVC often is a rapidly

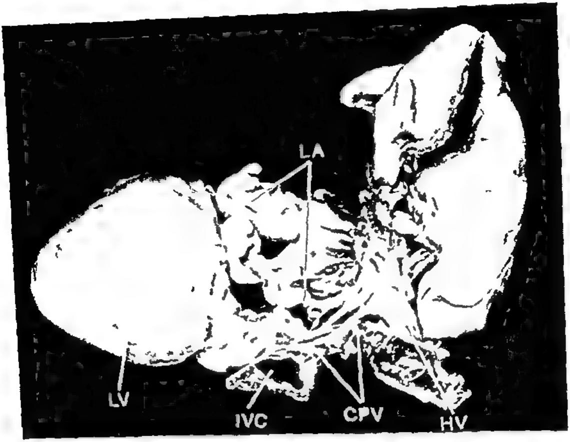


Fig 2 Probabl common pulmonary vein (*CPV*) is atretic cordlike remnant that runs from horizontal vein (*HV*) dorsally to inferior surface of left atrium (*LA*) ventrally passing immediately to left of inferior vena cava (*IVC*) This location corresponds to that of the CPV early in its development in normal human embryos

and the carina posteriorly as the vein ran right ward and superiorly to the RSVC (Fig 5 *e*)

In the azygos type of isolated TAPVC both cases had severe obstruction (Table IV) In one case there was marked hypoplasia of the connecting vein the diameter being less than 1 mm (Fig 5 *f*) The other case had marked stenosis at the entry of the azygos into the RSVC

In the coronary sinus type none had obstruction An example of *familial TAPVC* occurred in this type A 1 ½ month old white male infant (A62 238) had a sibling who died 2 years previously at 15 days of age from subdiaphragmatic TAPVC

In the subdiaphragmatic type of isolated TAPVC all 14 cases were thought to be obstructed (Table IV) The anomalous venous pathway always led to the ductus venosus and then continued as follows to the left portal vein in eight cases (Fig 5 *g*) to the inferior vena cava in three cases (Fig 5 *h*) to both the left portal vein and the inferior vena cava in one case to the left gastric vein in 1 case (Fig 5 *i*) and with no continuation whatever (atresia) in one case

Atresia of the anomalous venous pathway is rare but has been documented by Lucas and Nakib and their co workers In our case total obstruction was documented by postmortem angiography (Fig 6) as well as by careful dissection (Fig 7) The ductus venosus was atretic at two critical points resulting in total obstruction (see inset Fig 7) (1) between the anomalous pathway and the left portal vein and (2) between the anomalous pathway and the inferior vena cava This patient was a male identical twin the other twin was normal How it was possible for this patient to survive for 6 days postnatally was not established with certainty (Perhaps pulmonary bronchial venous anastomoses may have facilitated this infant s postnatal survival)

Stenosis at the diaphragm was present in three cases of the subdiaphragmatic type produced by extrinsic pressure on the anomalous venous path

Table VI Nonisolated TAPVC without heterotaxy

Autopsy No	Site of TAPVC	Obstruction of TAPVC	Age at death	Types of CHD	Extracardiac anomalies
Supracardiac					
A63 215	Snowman	Yes	2 wk	Mitral atresia absent LV D TGA pulmonary atresia	
A71 172	Snowman	No	47 days	ASD II dextrocardia retrobronchial LPA	Agenesis of right lung vascular bronchial compression agenesis of right kidney
A61 92	RSVC	No	24 days	Large ASD II vascular sling	Klippel Feil syndrome atretic right external auditory meatus and facial palsy
A71 60	RSVC	No	17 mo	Tricuspid atresia (type IC) common atrium	Cat's eye syndrome extrahepatic biliary atresia imperforate anus rectovaginal fistula accessory spleens (5)
Cardiac					
MR 6	RA	No	5 mo	Atretic RSVC LSVC to CoS mitral atresia severe hypoplasia of LA and LV DORV with BC PS inf and valvar	
A69 142	RA	No	19 yr	Tetralogy of Fallot LSVC to CoS to RA absent lt innom vein small PDA	
A68-82	RA	No	3 days	Left juxtaposition of atrial appendages LSVC to CoS to RA D TGA small PDA rt aortic arch	
MR 28	CoS	No	Stillborn	ASD II DILV overriding TV DORV BC PS inf and valvar	
MR 53	CoS	No	11 9/12 yr	Intact atrial septum multiple (3) VSD LSVC to CoS to RA	Hypoplastic left lung
A72 122	CoS	No	1 5/12 yr	ASDs II (2) LSVC to CoS to RA aberrant rt subclavian retrobronchial LPA dextrocardia	Agenesis of right lung vascular bronchial compression tracheobronchitis both kidneys right sided
MR 59 (A)	CoS	No	12 hr	Common atrium LSVC to CoS to RA tricuspid stenosis VSD (2) II TGA BC I S (inf)	Conjoined twin thoracopagus
Subdiaphragmatic					
MR 59 (B)	IVC	Yes	12 hr	LSVC to CoS to RA mitral stenosis DORV BC PS (inf) PDA	Conjoined twin thoracopagus

Abbreviations ASD II = secundum type of atrial septal defect BC = bilateral conus (subaortic and subpulmonary) CHD = congenital heart disease CoS = coronary sinus DILV = double inlet left ventricle DORV = double outlet right ventricle D TGA = dextro transposition of the great arteries (aortic valve to right of pulmonary valve) inf = infundibular LPA = left pulmonary artery LSVC = left superior vena cava LV = morphologically left ventricle PDA = patent ductus arteriosus PS = pulmonary stenosis RA = morphologically right atrium RSVC = right superior vena cava TV = tricuspid valve VSD = ventricular septal defect Tricuspid atresia type IC = with normally related great arteries and relatively large nonobstructive VSD

stenosis (hypoplasia) of the opening of the left innominate vein into the RSVC (Fig 5 *b*) In one of these cases for example the opening of the left innominate vein into the RSVC measured only 2 mm in diameter and there was marked poststenotic dilatation of the RSVC opposite the stenotic orifice of the left innominate vein No cause for this type of venous ostial stenosis was found

In the RSVC type of isolated TAPVC, four had obstruction of the anomalous venous pathway (67 per cent Table IV) Two cases had severe stenosis at the point of entry of the anomalous connecting vein into the RSVC (Fig 5, *c*) In the third case there was stenosis (hypoplasia) of the anomalous venous pathway, both of the part that ran within the right lung and of the part that ran through the mediastinum medial to the right lung to connect with the RSVC (Fig 5, *d*) In the fourth case, another type of arteriobronchial vise was found the connecting vein was compressed between the right pulmonary artery anteriorly

Table VII —cont d

Autopsy No	*Site of TAPVC*	*Obstruction of TAPVC*	*Age at death*	*Types of congenital heart disease*
Polysplenia and rudimentary spleen—supracardiac				
A67 216	Lt Innom V	Yes	31 days	Reverse "snowman" (hypoplastic rt. vertical vein to lt innom V to LSVC to LA) abnormal connection with normal drainage CAVC *l* loop marked hypoplasia of rt sided LV DORV with *l* MGA BC pulmonary atresia closing rt -sided PDA rt Ao arch dextrocardia
A67 101	Lt Innom V	No	4 days	"Snowman" variant—TAPVC with paraesophageal vertical vein that passed up middle of body to lt innom v rt -sided juxtaposition of atrial appendages situs solitus of atria *l* loop DORV with *d* MGA, PS (inf and valvar) common atrium (absent septum I) without CAVC
A51 173	RSVC	Yes	" 1/2 mo	LSVC to CoS to RA CAVC with mitral atresia DORV with *d* MGA BC PS (inf)
Polysplenia and rudimentary spleen—cardiac				
A68-66	RA	No	7 1/4 yr	ASD secundum small subaortic VSD 2 accessory spleens (75/6? gm)
A67	RA	No	1? 7/12 yr	Situs inversus totalis dextrocardia 2 rt -sided spleens (150/90 gm) interrupted IVC with azygos continuation CAVC male Turner syndrome
A54 9?	CoS	No	11 days	Mitral atresia hypoplastic LV DORV with *d* MGA BC aortic stenosis (inf and valvar) interrupted Ao arch 11 spleens (18/10 gm)
C?0-156	CoS	No	2 days	Virtually intact atrial septum due to prominent left venous valve hypoplastic lt. heart
Polysplenia and rudimentary spleen—subdiaphragmatic				
A68-151	Lt gastric v	Yes	6 days	Mitral atresia hypoplastic LV muscular VSD bicuspid Ao V and preductal coarc aberrant rt subclavian T E fistula hemivertebrae
Heterotaxy with normal spleen				
A66-284	Lt gastric v & portal v	Yes	9 mo	Bilat SVC probable inversion of atria complete CAVC DORV with *d* MGA BC PS (inf and valvar) symmetrical liver common mesentery

(2) a "snowman" that also had anomalous connections from the right upper lobe to the RSVC

(3) the left lung draining via a "snowman" and the right lung draining into the coronary sinus

(4) subdiaphragmatic to the portal vein with a small "snowman" and

(5) subdiaphragmatic to the portal vein with connections from the right upper lobe to the RSVC

The latter two cases were thought to be obstructed

The diagnosis of obstruction in isolated TAPVC is not always easy Injection into the main pulmonary artery often results in the loss of considerable contrast through a patent ductus arteriosus down the descending thoracic aorta This results in poor visualization of the anomalous venous pathway and also makes recognition of obstruction of this pathway virtually impossible Hence selective injection into the left or right pulmonary artery is suggested in this situation in order to minimize the loss of contrast through the ductus thereby making adequate visualization of the venous pathway and of any obstruction more likely

When the obstruction of the anomalous venous pathway is very severe cardiac catheterization and angiocardiography may actually be diagnostically misleading as occurred in the case with atresia of the anomalous venous pathway (Figs 6 and 7) The chest x ray (Fig 8) showed a normal sized heart and "ground glass" lung fields accurately suggesting the correct diagnosis But at cardiac catheterization no localized oxygen step up was found and the anomalous venous pathway was never visualized angiocardiographically—both because this pathway was atretic This

Table VII Nonisolated TAPVC with heterotaxy syndrome

Autopsy No	Site of TAPVC	Obstruction of TAPVC	Age at death	Types of congenital heart disease
Asplenia—supracardiac				
A68 272	RSVC	Yes	2 mo	Dextrocardia TAPVC compressed between RPA ant and rt bronchus post RSVC to rt sided LA (abnormal connection normal return) common atrium complete CAVC *l* loop normally related GA s aortic valvar atresia double aortic arch, bilateral PDA
A51 92	RSVC	No	1 mo	CAVC with mitral atresia *d* loop DORV with *d* MGA BC with inf PS rt Ao arch
A59 150	RSVC	No	8 days	Complete CAVC *d* TGA pulmonary atresia (inf and valvar) rt Ao arch small PDA familial asplenia (also present in brother A61 176)
A61 2u4	RSVC	No	2 1/2 yr	Dextrocardia situs inversus common atrium CAVC *l* loop DORV with *l* MGA BC with PS (inf) rt Ao arch
A66 10u	RSVC	No	9 2/3 yr	TAPVC to RSVC to LA (abnormal connection normal return) dextrocardia complete CAVC *d* loop DORV with *d* MGA BC with PS (inf & valvar) absent lt coronary ostium probable situs inversus
A64 76	LSVC	Yes	3 wk	LSVC to RA (lt sided) *d* loop single RV CAVC with mitral atresia DORV with *d* MGA s BC pulmonary atresia (valvar) splenic artery present (becoming gastroepiploic)
A5u-313	LSVC	No	7 wk	Dextrocardia situs inversus bilat SVC CAVC with tricuspid atresia double inlet LV anatomically corrected *l* MGA with BC PS due to small VSD
Asplenia—cardiac				
A66-76	RA	No	6 mo	Dextrocardia RA (lt sided) bilat SVC complete CAVC *d* loop *d* TGA pulmonary atresia MPA not identified rt Ao arch BC imperforate anus posterior urethral valves
A61 176	RA	No	11 days	TAPVC to RA part of common atrium above IVC common atrium CAVC single RV DORV *d* MGA pulmonary atresia PDA rt Ao arch familial asplenia (brother of A59 150)
Asplenia—subdiaphragmatic				
A63 122	Portal vein	Yes	7 wk	Bilat SVC complete CAVC *l* loop DORV with *l* MGA BC PS rt Ao arch
A57 93	Gastric vein and ductus venosus	Yes	6 days	Dextrocardia atrial inversion CAVC *l* loop DORV with *l* MGA BC PS (inf and valvar)
Au4 J16	IVC	Yes	7 wk	Complete CAVC with severe MS and LV hypoplasia *d* loop DORV with *d* MGA BC PS (inf and valvar) rt Ao arch rt ureteral valve and rt hydroureter
A71 262	Ductus venosus	Yes	11 wk	CAVC with mitral atresia single RV DORV with *d* MGA BC rt Ao arch IVC lt sided with liver rt sided (hepatic IVC discordance)
A72 120	Left portal vein	Yes	4 1/2 days	Complete CAVC with MS *d* transposed Ao with absence of MPA rt Ao arch

Abbreviations As in Table IV except for the following Ao = aortic ASD I = primum atrial septal defect CAVC = common atrioventricular canal *d* MGA = *d* malposition of great arteries (aortic valve to right of pulmonary valve) GA s = great arteries IVC = inferior vena cava LA = morphologically left atrium lt innom v = left innominate vein MPA = main pulmonary artery MS = mitral stenosis RV = morphologically right ventricle T E = tracheoesophageal

ways as it passed through the diaphragm (Fig 5 g)

TAPVC in twins occurred twice in the subdiaphragmatic type Both were believed to be identical and in both pairs the co twin was normal

The mixed type of TAPVC was always isolated (Table III) and was occasionally obstructed (Table IV) There were five cases with anomalous connections at more than one level

(1) a snowman ' also with a small connection to the coronary sinus,

led to the erroneous conclusion that the patient probably had lung disease not congenital heart disease One of the lessons we learned at this autopsy (Figs 8 and 7) was that we should have believed the plain chest x ray (Fig 8) and should not have allowed the negative findings at cardiac catheterization and angiocardiography to mislead us In retrospect we appreciated that with highly obstructed TAPVC one should *expect* negative cardiac catheterization and angiocardiography

How reliable are the pressure data concerning the presence or absence of obstruction of the anomalous venous pathway? As Table V shows concerning isolated TAPVC when the pulmonary arterial pressure was systemic or suprasystemic obvious anatomic obstruction of the anomalous venous pathway was usually present in 17/23 cases 74 per cent However there were six cases with systemic or suprasystemic pulmonary arterial pressures in which no obstruction was found (26 per cent) it should be added that the pulmonary histology of these six cases did not show pulmonary vascular obstructive changes

Pulmonary arterial pressures less than systemic usually indicated the absence of obstruction of the anomalous venous pathway in 87 per cent (Table V) However there were two cases with postmortem proved obstruction of the anomalous venous pathway in which the pulmonary arterial pressures were less than systemic (Table V) These pulmonary pressures were nonetheless very elevated (112/40 and 88/51 mm Hg) although less than systemic—a point which merits emphasis

Thus, when obstruction was present the pulmonary arterial pressures always were elevated However of all the cases with markedly elevated pulmonary arterial pressures only about three quarters (74 per cent) had obvious anatomic obstruction of the pulmonary venous return Hence about one quarter of the cases of severe pulmonary hypertension are not explained

Can the atrial septum be obstructive? This is possible but infrequent we think In one case (A70-221) for example pressures in the pulmonary artery and right ventricle were suprasystemic but there was no obstruction of the snow man type of TAPVC and there was no histologic evidence of pulmonary vascular obstruction There was a 4 mm mean pressure gradient on pullback from the left atrium (2 mm Hg) to the right atrium (6 mm Hg) strongly suggesting the presence of obstruction at the level of the atrial septum The atrial septum appeared to be the only site of obstruction (gradient of 3 to 4 mm Hg on pullback) in three of 38 catheterized and autopsied cases of isolated TAPVC (8 per cent)

Would *balloon atrial septostomy* as advocated by several groups [11,12] have lowered the right heart pressure? Since this was not done we are unable to answer this question While there is no doubt that more data are needed concerning the possible role of balloon atrial septostomy in TAPVC we are inclined to think that this

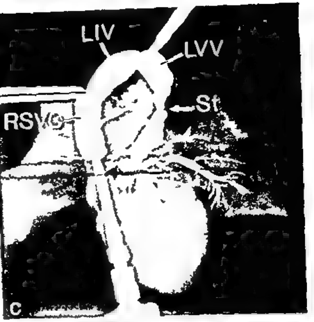
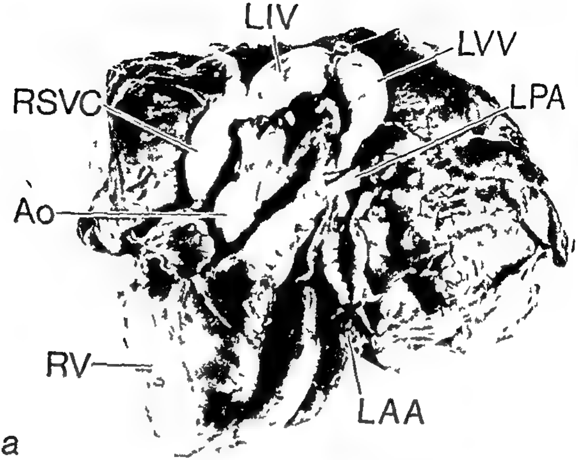


Fig 3c Postmortem angiogram showing stenosis (*st*) of left vertical vein (*LVV*) where it passes posteriorly to left pulmonary artery *Ao* = aorta *LA* = left atrium *LAA* = left atrial appendage *LIV* = left innominate vein *LL* = left lung *LV* = left ventricle *LVV* = left vertical vein *RSVC* = right superior vena cava *RV* = right ventricle

Table VIII Types of TAPVC with and without heterotaxy

	Heterotaxy		*Without heterotaxy*		*Total series*	
Types of TAPVC	*No*	*%*	*No*	*%*	*No*	*%*
Supracardiac	10	44	32	46	42	45
Cardiac	6	26	18	26	24	26
Subdiaphragmatic	7	30	15	21	22	24
Mixed	0	0	5	7	5	[illegible]
Totals	23	100	70	100	93	100



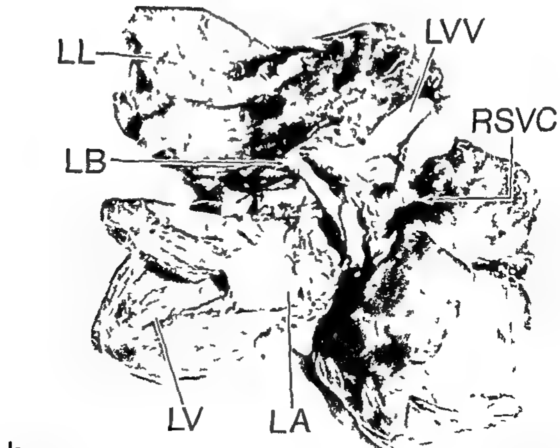


Fig 3a b Snowman type of TAPVC with obstruction of the anomalous venous pathway which is compressed between *left pulmonary artery (LPA)* anteriorly and *left bronchus (LB)* posteriorly *a* is anterior view and *b* is posterior view of specimen of heart and lungs

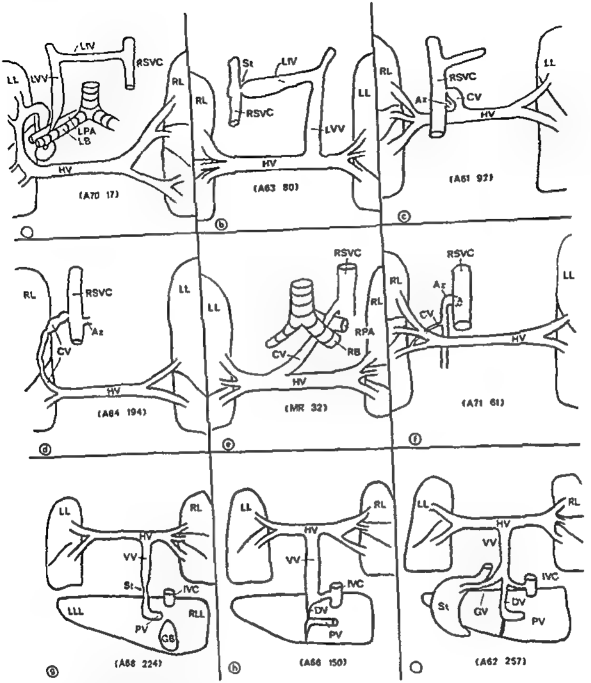


Fig [illegible] Diagrams of various types of obstruction of anomalous venous pathway in TAPVC *a* In "snowman," left vertical vein (*LVV*) between left pulmonary artery (*LPA*) anteriorly and left bronchus (*LB*) posteriorly *b* in "snowman," stenosis at junction of left innominate vein (*LIV*) with right superior vena cava (*RSVC*) and poststenotic dilatation of *RSVC* *c* in RSVC type stenosis at junction of connecting vein (*CV*) with RSVC *d*, in RSVC type stenoses of CV both of intrapulmonary and extrapulmonary portions *e* in RSVC type compression of CV between carina and right bronchus (*RB*) posteriorly and right pulmonary artery (*RPA*) anteriorly *f* in azygos (*Az*) type extreme hypoplasia (stenosis) of *CV* between right lower lobe pulmonary vein and Az vein *g* in subdiaphragmatic type stenosis of vertical vein (*VV*) by diaphragmatic compression (*St*) and connection to portal vein (*PV*) necessitating passage of pulmonary venous blood through hepatic sinusoids *h* in subdiaphragmatic type passage of blood from left lung (*LL*) and right lung (*RL*) via horizontal vein (*HV*) to (*VV*) and thence via ductus venosus (*DV*) to inferior vena cava (*IVC*) the segment of *DV* between the *VV* and *PV* being atretic and *i* in the subdiaphragmatic type the *VV* may connect via large gastric vein (*GV*) to stomach (*St*) and via *DV* both to *PV* and *IVC* *GB* = gall bladder *LLL* = left lobe of liver *RLL* = right lobe of liver

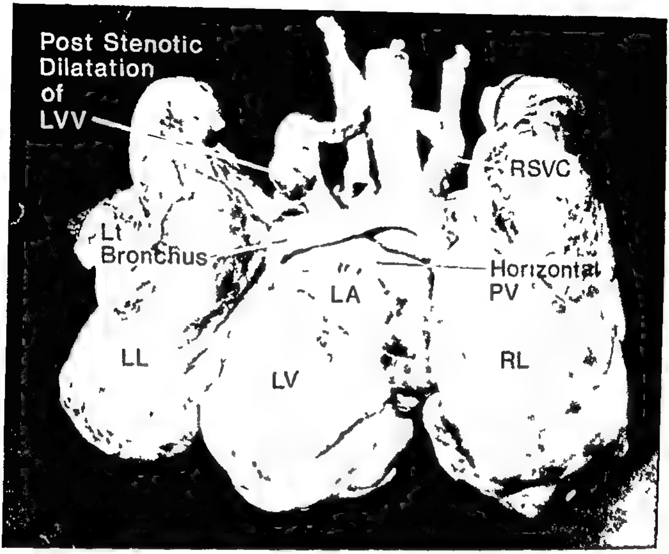


Fig 4 Posterior view of obstructed snowman type of TAPVC Note the poststenotic dilatation of the left vertical vein (*LVV*) above the level of the left mainstem bronchus and the anastomosis of the horizontal pulmonary vein (*PV*) to the left atrium (*LA*)

procedure should be tried, particularly when there is a distinct pressure gradient between the atria It is hoped that the removal of obstruction at the atrial septal level will make it possible at least in some cases to defer surgery until the patient is older and the chances of surgical success at most centers are greater However, the thickening and partial muscularization of septum primum that occurs with an obstructive patent foramen ovale may make it more difficult to obtain a satisfactory tear of septum primum

Newer approaches such as hypothermic arrest,[14] may well facilitate surgical correction of TAPVC with an acceptably low mortality rate in early infancy

Nonisolated TAPVC These are the cases that are usually omitted in accounts of TAPVC in view of their complexity, and because the diagnostic and surgical problem is very different from isolated TAPVC Despite their complexity, we think that these cases should not be omitted because they constitute more than one third of the cases of TAPVC (38 per cent Table II) Because of lack of space discussion of this complex and fascinating group will be very limited (It is suggested that the interested reader study Tables VI and VII with care)

Without heterotaxy There were 12 cases (13 per cent of the series, Table II) that did not have the asplenia[15] or heterotaxy[16] syndrome and the associated congenital heart disease tended to be complex (Table VI) double outlet right ventricle with pulmonary stenosis three cases *d* transposition of the great arteries, three mitral atresia two, tricuspid atresia, one double inlet left ventricle one, and vascular sling one case

The extracardiac anomalies also were occasionally complex (Table VI) cat s eye syndrome[17], conjoined ("Siamese) twins, and agenesis of the right lung with anomalous venous drainage from the left lung resulting in what might be called ' total partial anomalous pulmonary venous return (A71 172 and A72 122, Table VI)

The rarest finding in this group probably is

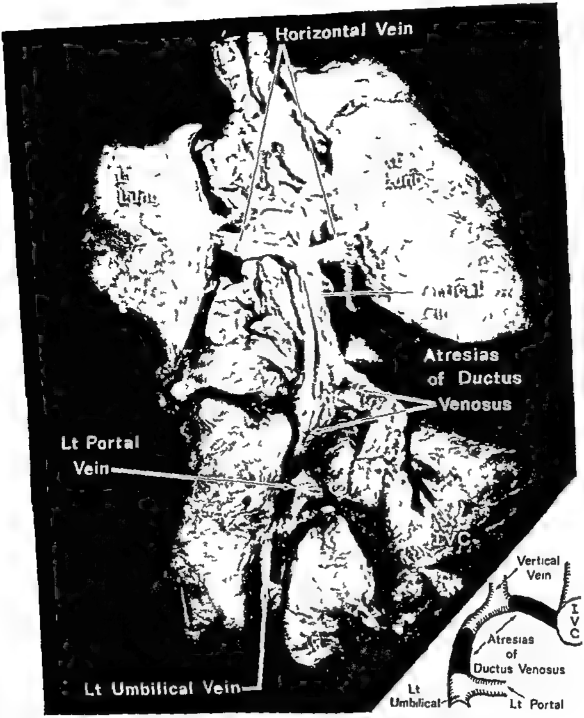


Fig 7 *TAPVC* below diaphragm with total obstruction of vertical vein by two atresias of the ductus venosus preventing communication either with the left portal vein or with the inferior vena cava *(IVC)*

mitral atresia (4/22 cases Table VII) mitral stenosis (2 cases) and tricuspid atresia (1 case) due to narrowing or occlusion of the left or right sides of the AV canal by endocardial cushion tissue

(f) familial asplenia occurred (A59 150 and A61 176 Table VII) and

(g) discordance between the sidedness of the inferior vena cava and the sidedness of the liver (A71 262 Table VII) indicating that in some

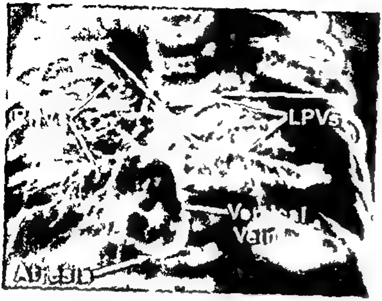


Fig 6 Postmortem angiogram showing *TAPVC below the* diaphragm with total obstruction due to atresia of the vertical vein at the ductus venosus *LPV's* = left pulmonary veins *RPV's* = right pulmonary veins

TAPVC with an intact atrial septum (MR 53, Table VI) There was marked dilatation of the cephalic portion of the persistent left superior vena cava (Fig 9) that drained into the coronary sinus along with the anomalous pulmonary veins The intact atrial septum, multiple ventricular septal defects, and hypoplasia of the left lung are shown in Fig 10 Hastreiter and associates[18] published a somewhat similar case TAPVC with an intact atrial septum and a patent ductus arteriosus

With heterotaxy Some of the more interesting findings that emerged from this complex and fascinating group of 23 cases (25 per cent of the series Tables II and VII) are the following

1 Our initial impression was that TAPVC in the heterotaxy syndrome usually is subdiaphragmatic, but this was not supported by the findings Indeed, the percentages of supracardiac, cardiac, and subdiaphragmatic cases were remarkably similar in the heterotaxy syndrome, in the nonheterotaxic group and in the series as a whole (Table VIII)

2 Another initial impression, namely, that TAPVC in the heterotaxy syndrome usually is obstructed, also proved to be incorrect—although not as wrong as the previous erroneous impression mentioned above not obstructed 12 cases, 52 per cent, and obstructed 11 cases 48 per cent

3 In the heterotaxy syndrome, the presence of TAPVC and the existence of obstruction of the anomalous venous pathway both may be obscured by pulmonary outflow tract obstruction—stenosis or atresia—which is frequent in this syndrome For example, in our case of the "asplenia" syndrome with a normal spleen (A66 284 Table VII), the presence of TAPVC and of obstruction of the anomalous pathway both became evident only after a Waterston anastomosis had been performed

4 A unique case of TAPVC with a virtually intact atrial septum (only one tiny opening less than 1 mm in diameter) and a hypoplastic left heart occurred with polysplenia (C70 156 Table VII) In this case of TAPVC to the coronary sinus a very prominent left venous valve occluded the foramen ovale (Fig 11) How a prominent left venous valve can occlude the interatrial communication is indicated by Fig 12

5 Two interesting "snowman variants" were found in this series A "reverse snowman" was present in one case of polysplenia (A67 216 Table VII) right vertical vein to left innominate vein to left superior vena cava to left sided morphologically left atrium This patient also illustrates the difference between total anomalous pulmonary venous *connection* (present in this case) and total anomalous pulmonary venous *drainage* (not present in this case) In this case and two others (A66 105 and A68 272 Table VII) the connection is abnormal, but the drainage is normal

The other 'snowman' variant is rare (A67 101, Table VII) The vertical vein that passes cephalad to join the left innominate vein was *midline* (not left sided)—a paraesophageal vein

6 Since the asplenia syndrome is an integral part of the problem of TAPVC and vice versa (Tables II and VII), the following points of interest concerning asplenia merit mention

(a) complete common AV canal can co exist with normally related great arteries (A68 272 Table VII),

(b) aortic valvular atresia can occur (A68 272),

(c) a double aortic arch can occur in asplenia (A68 272)

(d) in the asplenia syndrome, double outlet right ventricle is the rule (9/13 cases 69 per cent) not transposition of the great arteries (2 cases, 15 per cent)*,

(e) complete common AV canal occurred with

*Transposition of the great arteries is used with the meaning that the aorta arises above the morphologically right ventricle and the pulmonary artery originates above the morphologically left ventricle

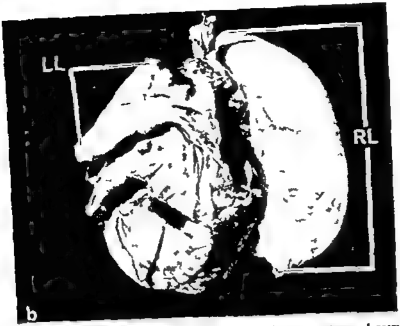


Fig 10b Posterior view showing hypoplasia of left lung (*LL*) and compensatory enlargement of right lung (*RL*)

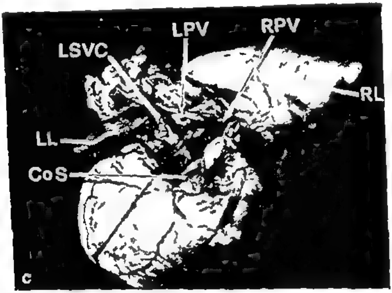


Fig 10c Posterior view showing that the left pulmonary vein (*LPV*) right pulmonary vein (*RPV*) and left superior vena cava (*LSVC*) all drain into the coronary sinus (*CoS*) The white arrow at the end of the *CoS* leader passes through *CoS* ostium into *RA*

the question is How true is this statement? Specifically is the surgeon's friend —the horizontal vein—always present waiting to be anastomosed to the left atrium? Briefly the answer is Almost always

There is no horizontal vein in the following situations (1) TAPVC to the right atrium (2) TAPVC to the coronary sinus and (3) occasionally in the mixed type

1 *In TAPVC to the right atrium* there is no discrete horizontal vein that can be anastomosed to the left atrium in the usual way The pulmonary veins connect directly with the dorsal wall of the right atrium without forming a horizontal vein From the anatomic standpoint the procedure of choice would appear to be atrial septectomy followed by tunnelling of the pulmonary veins into the left atrium

Fig 8 Posteroanterior chest x ray showing normal heart size and "ground glass" lung fields accurately suggesting *TAPVC* below the diaphragm with obstruction (same case as in Figs 6 and 7)

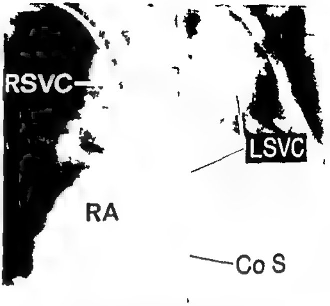


Fig 9 Angiogram into persistent left superior vena cava (*LSVC*) showing curious and poorly understood dilatation of cephalic end of *LSVC* in case of *TAPVC* to the coronary sinus (*CoS*) to right atrium (*RA*) with intact atrial septum and multiple ventricular septal defects.

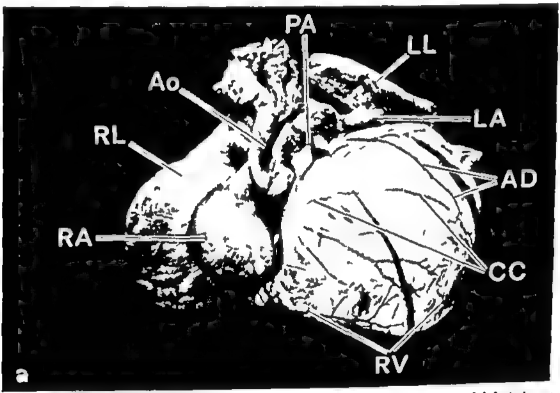


Fig 10a *TAPVC* to coronary sinus with intact atrial septum and multiple ventricular septal defects (same case as in Fig 9) External frontal view showing marked hypertrophy and enlargement of the right atrium (*RA*) and right ventricle (*RV*) A prominent conus coronary artery (*CC*) joins the anterior descending coronary artery (*AD*)

cases the right or left sidedness of the inferior vena cava may not necessarily indicate the basic type of visceroatrial situs with accuracy in all cases of the heterotaxy syndrome [19]

Surgical considerations As an initial approximation, it may be said that from the surgeon's standpoint, it does not matter what type of TAPVC is present, or whether it is obstructed or not, because there always is a horizontal vein running from hilum to hilum, and it is this horizontal vein that is anastomosed to the dorsal wall of the left atrium as is seen in Fig 4 Now

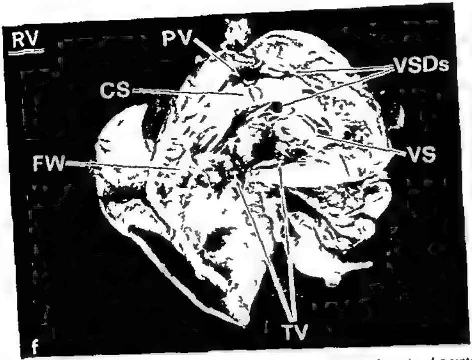


Fig 10f Opened *RV* showing marked hypertrophy and enlargement, and multiple ventricular septal defects (*VSDs*) The *VSD* beneath the crista supraventricularis (*CS*) is subdivided into two parts by insertions of the tricuspid valve (*TV*) Above the *CS* and to the left of the pulmonary valve there is a conal septal defect (white probe)

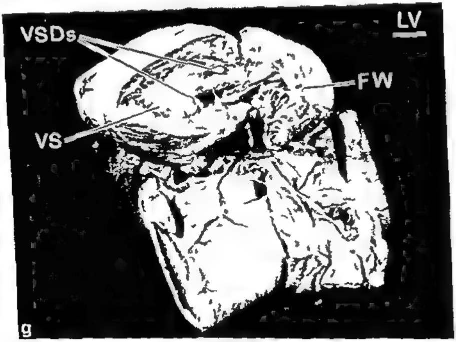


Fig 10g Opened left ventricle (*LV*) shows white probes through the lower subcristal membranous *VSD* and through the higher supracristal muscular *VSD* *FW* = free wall *VS* = ventricular septum (MR 53 Table VI)

struction of the pulmonary inflow tract rather analogous to reconstruction of the pulmonary outflow tract in tetralogy of Fallot with pulmonary atresia and in truncus arteriosus communis Such a reconstruction would clearly be more formidable than the usual anastomosis However this was the only case in this series of 93 patients in whom the anatomy posed this type of problem in achieving correction of the TAPVC

Agenesis of the right lung with anomalous

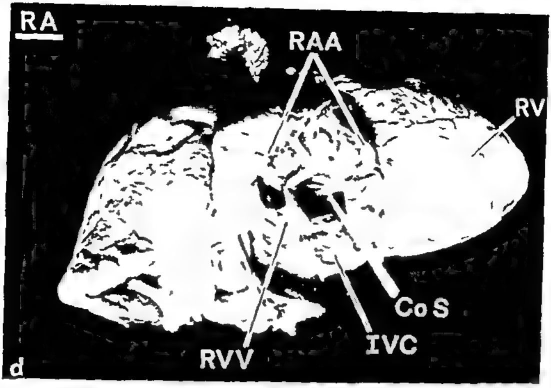


Fig 10d Opened *RA* showing hypertrophied and enlarged right atrial appendage (*RAA*) prominent muscularized right venous valve (*RVV*) inferior vena cava (*IVC*) and white pointer in enlarged ostium of *CoS*

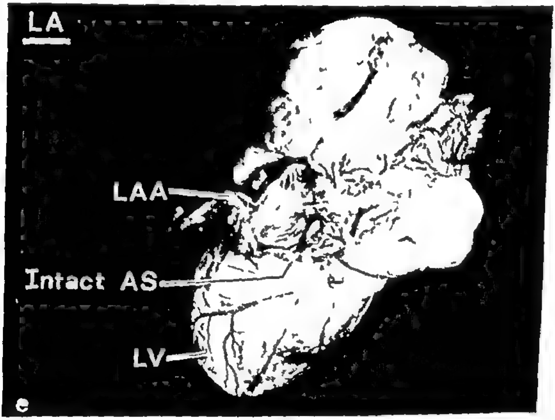


Fig 10e Opened left atrium (*LA*) showing intact atrial septum (*AS*)

2 *In TAPVC to the coronary sinus* there is no discrete horizontal vein However the coronary sinus can function as a horizontal vein from the surgical standpoint and a large window can readily be made between the coronary sinus and the left atrium by a technique that has been described elsewhere [19]

3 *In the mixed type of TAPVC* occasionally there is no horizontal vein This pertained in only one of our five cases of mixed TAPVC the left lung drained via a snowman and the right lung drained into the coronary sinus Perhaps an anastomosis could be fashioned between the left and right pulmonary veins and left atrium—recon

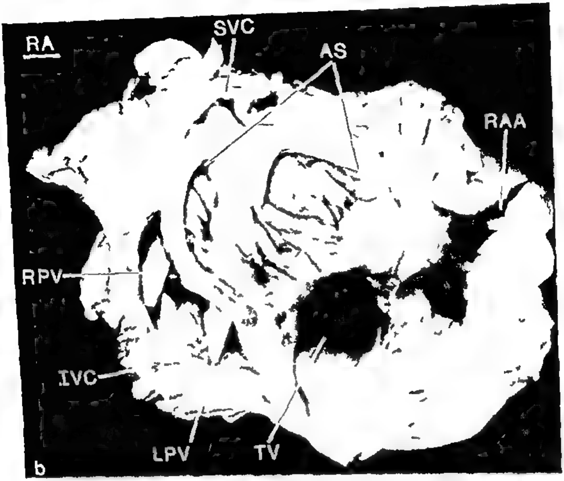


Fig. 11b. Opened *RA* showing white pointers leading from the right pulmonary veins (*RPV*) and left pulmonary veins (*LPV*) that open into the markedly *enlarged coronary sinus* and thence into *RA* immediately above the inferior vena cava (*IVC*). The bizarre morphology of the right atrial septal surface (*AS*) is due to a prominent and highly obstructive left venous valve that occludes the foramen ovale.

in the first year of life improved from 67 per cent (two of three patients, 1968 to 1969) to 16 per cent (one of six patients, 1970 to 1972). Similarly, Barratt-Boyes[3] reported in 1973 a mortality rate for surgical correction of TAPVC in the first year of life of 18 per cent (two of 11 patients, July, 1969, to September, 1972). Both of the latter deaths occurred in infants less than 6 months of age.[3] In 1974, Castañeda and associates[22] reported a mortality rate for the surgical correction of TAPVC utilizing deep hypothermia during the first 3 months of life of only 25 per cent (one of four infants, January, 1973, to March, 1974). Castaneda successfully corrected the condition in infants of 7 days, 20 days, and 30 days of age, two to the coronary sinus and one supracardiac. The results of Castaneda and his colleagues may be updated (as of July 10, 1975) as follows: 11 patients with TAPVC were operated upon with 3 deaths (27 per cent mortality rate). The ages at operation of these 11 patients varied from 36 hours to 7 months, 8 being within the first month with only 2 deaths. In detail, 6 were supracardiac with 2 deaths, 2 were to the coronary sinus with no deaths, and 3 were subdiaphragmatic with 1 death. It is hoped that the findings of the present study will facilitate further reduction in the mortality rate from TAPVC.

Summary

Total anomalous pulmonary venous connection (TAPVC) is failure of development of the common pulmonary vein with consequent persistence and enlargement of embryonic collaterals between the lungs and the systemic veins. In the great majority (91 of 93 autopsied cases, 97 per cent), no remnant of the common pulmonary vein was found, supporting the concept of agen

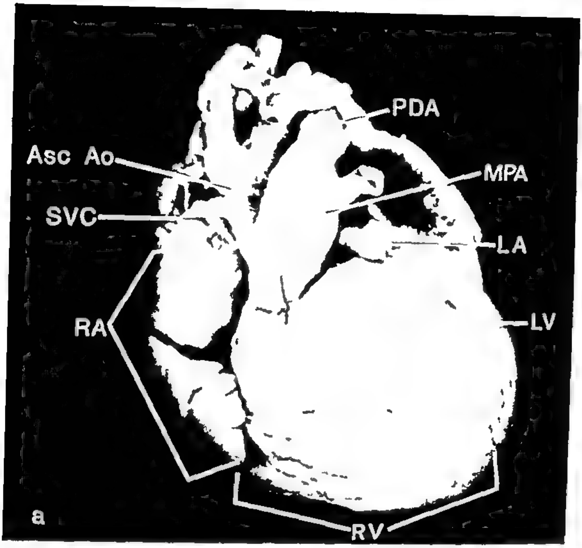


Fig 11a TAPVC to coronary sinus with polysplenia (C70 156 Table VII) prominent left venous valve virtually intact atrial septum and hypoplastic left heart External frontal view showing marked hypertrophy and enlargement of right atrium (RA) and right ventricle (RV)

pulmonary venous drainage from the left lung merits special mention because of vascular bronchial compression—like a vascular ring—that appeared important in leading to death in both of our cases (A71 172 and A72 122, Table VI) Agenesis of the right lung results in extrinsic dextrocardia The normal left aortic arch compressed the tracheobronchial tree anteriorly and superiorly The large left pulmonary artery (LPA) passed *posteriorly* to the left bronchus (normally the LPA is anterior to the left bronchus), compressing the *left* bronchus posteriorly and inferiorly The ligamentum arteriosum and in one case an aberrant right subclavian artery facilitated the external tracheobronchial compression produced by this vascular vise In addition to surgical correction of the TAPVC steps to relieve the vascular tracheobronchial compression also appear necessary such as (1) division of the ligamentum arteriosum, (2) division of the aberrant right subclavian artery, if present, and (3) 'aortopexy'—attaching the aorta anteriorly in a subcostal or substernal location in order to reduce the anterosuperior tracheobronchial compression The possibility of running a graft from the main pulmonary artery to the distal left pulmonary artery, with ligation of the left pulmonary artery proximally, was considered From the anatomic standpoint this appeared technically difficult because of the retrobronchial location of the left pulmonary artery in both of our cases Thus, with agenesis of the right lung the 'vascular ring' problem seems as important as the TAPVC, suggesting in such cases, both problems should be dealt with surgically

In conclusion surgical results in the management of TAPVC have improved considerably since the study of Gathman and Nadas[3] in 1970 For example Kirklin[20] reported in 1973 that his mortality rate for surgical correction of TAPVC

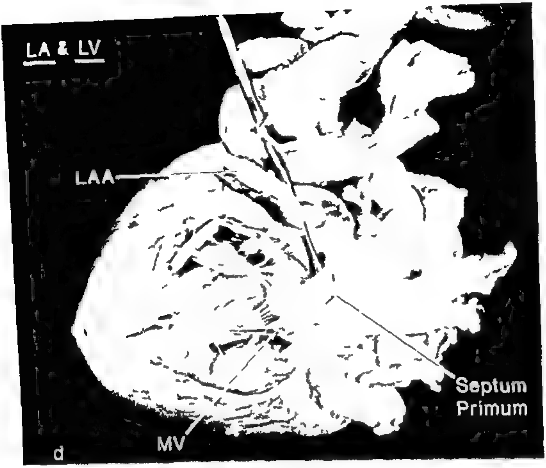


Fig 11d Opened left atrium (*LA*) and left ventricle (*LV*) showing normal morphology of the left atrial septal surface including septum primum and a hypoplastic but not malformed left heart

death in the total series of 93 cases being only 7 weeks ranging from stillbirth to 19 years The various sites of obstruction of the anomalous venous pathway were presented in detail and their angiocardiographic diagnosis was considered At catheterization in isolated TAPVC when pulmonary arterial pressure was systemic or suprasystemic obstruction of the anomalous venous pathway was present in three quarters of such cases (74 per cent) When pulmonary arterial pressure was less than systemic obstruction was usually absent (87 per cent) Occasionally the atrial septum appeared to be the only site of obstruction (gradient of 3 to 4 mm Hg on pullback) as in three of 38 catheterized and autopsied cases of isolated TAPVC (8 per cent) In this situation balloon atrial septostomy appears to be indicated

Rare and unique cases found in this series merit mention intact atrial septum with multiple ventricular septal defects virtually intact atrial septum due to prominent left venous valve with hypoplastic left heart total obstruction of the anomalous venous pathway at the ductus venosus familial TAPVC familial asplenia and a case of asplenia with common AV canal normally related great arteries aortic valvular atresia and double aortic arch

Surgical correction was considered The horizontal vein which is anastomosed to the left atrium was always present except in three situations (1) TAPVC to the right atrium (2) TAPVC to the coronary sinus and (3) in one case of mixed TAPVC In both cases of TAPVC with agenesis of the right lung vascular compression of the tracheobronchial tree—mimicking a vascular ring—was an important problem and its surgical management was considered From the anatomic standpoint TAPVC appears almost always to be surgically correctable

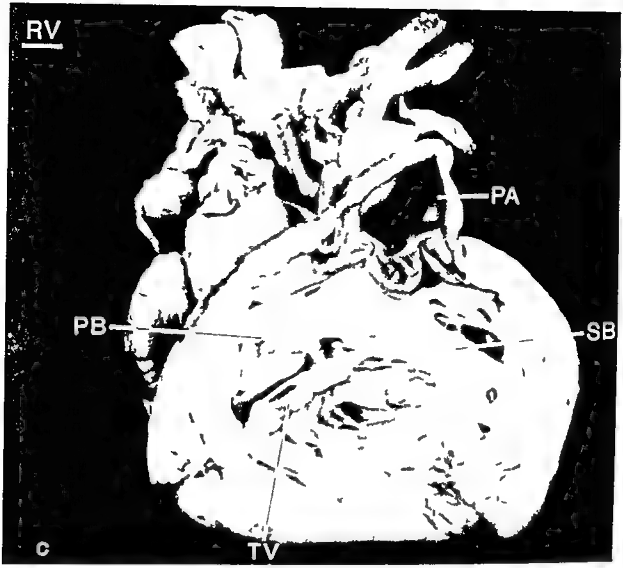


Fig 11c Opened RV showing hypertrophy and enlargement normal architecture and no ventricular septal defect

esis or involution of the common pulmonary vein Occasionally, a cordlike strand was found in the location of the common pulmonary vein (in three of 93 cases 3 per cent), supporting the concept of atresia of the common pulmonary vein

The order of frequency of the various types of TAPVC was left innominate vein ("snowman'), 26 per cent subdiaphragmatic, 24 per cent, coronary sinus 18 per cent, right superior vena cava, 15 per cent, right atrium, 8 per cent mixed 5 per cent, azygos, 2 per cent, and left superior vena cava, 2 per cent TAPVC occurred without other congenital heart disease (isolated TAPVC) in 62 per cent and with other types of congenital heart disease (nonisolated TAPVC) in 38 per cent Approximately two thirds of nonisolated TAPVC (23 of 35 cases, 66 per cent) was composed of the heterotaxy syndrome—asplenia (14 cases), rudimentary spleen and polysplenia (eight cases), and heterotaxy with a normally formed spleen (one case) The commonest type of isolated TAPVC was the snowman (20 of 58 cases 34 per cent) whereas the commonest types of nonisolated TAPVC were to the right superior vena cava and to the ductus venosus (both eight of 35 cases, 23 per cent) TAPVC directly to the right atrium was always nonisolated (seven cases, 8 per cent) However, in isolated and nonisolated TAPVC, the percentages of supracardiac, cardiac, and subdiaphragmatic were remarkably similar

Obstruction of the anomalous venous pathway was present in 30 of 58 cases of isolated TAPVC (52 per cent) and their median age at death was only 3 weeks In the 28 cases of isolated TAPVC without obvious anatomic obstruction of the anomalous venous pathway (48 per cent) the median age at death was 3 months TAPVC is often a rapidly lethal disease the median age at

The mechanics of widespread training of cardiopulmonary resuscitation A community project implemented by volunteers

Peggy Flax R N *
Tom Larke**
George Walser***
William Kaye M D ****
Herman Uhley M D
Marin County Calif

Within recent years there has been increased interest in the development of emergency care systems [1] and mobile coronary care units have appeared in several areas of the world There is now some consideration of augmenting emergency care systems by training the general public in the basics of cardiopulmonary resuscitation (CPR) Initially there was opposition by medical authorities to the widespread training of lay groups as the improper application of CPR posed a great many potential hazards However the Seattle experience in CPR training of the general public has been that citizens can be trained to perform CPR and provide life support whereas under ordinary circumstances of a life threatening emergency help would have arrived too late for an effective rescue One can project the potential benefit of a public trained in the use of CPR in a variety of emergency conditions such as heart attacks suffocation drowning electrocutions allergic reactions etc Thus the capability of a trained person to initiate CPR at the onset of a catastrophe may result in sustaining life and compensate for the length of the response time of the official rescue team

In Marin County across the Golden Gate Bridge north of San Francisco the CPR Committee of Marin County Heart Association initiated a program in 1973 to train its citizens in basic life support measures of CPR The project is carried on entirely by volunteer personnel and the cost of materials is borne by the Marin County Heart Association Previous training in CPR has been directed toward the goal of providing fire police and ambulance personnel with the basics of CPR according to the standards of the American Heart Association [12] However the new program was directed toward the training of two non professional groups The first group trained consisted of ninth grade high school students and the second group of citizens who had an interest in CPR usually because of a probable association with high risk individuals One thousand three hundred and sixty three persons in Marin County have been trained in CPR within the last year

Materials needed

Several different types of educational materials are essential for a successful program A classroom with adequate floor space blackboards a 35 mm slide projector a 16 mm sound movie projector and a screen are needed Adult and infant sized manikins that are able to demonstrate airway obstruction chest movement with ventilation and sternal movement with compression should be available in adequate numbers for the size of the group (Preferably one manikin for four to six students) Supplementary materials such as wall charts [13] wallet cards [14] and discussion guides are helpful to the students for further reference and review [15]

From the CPR Committee f the M rin Cou ty H rt Associat on
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Reprint requests t Herman Uhley M D Associate Chief of Medicine, in charg of Coron ry Care U t, Mount Zio Hosp tal a d Medical Ce ter P O Bo 7971 S Francisco C lif 941?0

*Present ddress 17 W Shore Dr Bel ed re Calif 94941

**Present address 103 Fin Dr F irf x Calif 94304

***Present address 557 Whit wood, Sa Raf l, C lif 94904

****Present address 40 M nana W y Pt. Reyes, Calif 949 6

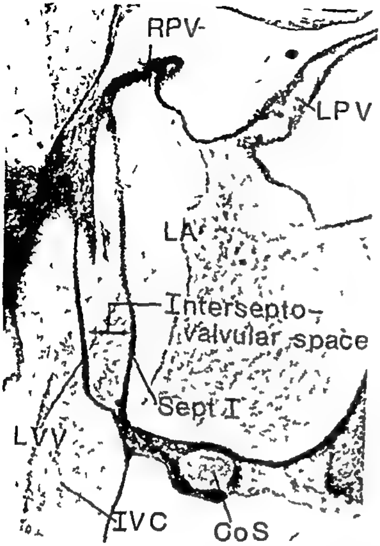

Fig 12 Frontal section of a human embryo to show how a prominent left venous valve (*LVV*) can occlude the interatrial communication resulting in one type of premature closure of *the foramen ovale* This embryo has an estimated age of 56 days 29 mm (Harvard Embryo No 914 stained with borax carmine and Lyons blue section 491 original magnification × 100) *CoS* = coronary sinus *IVC* = inferior vena cava *LA* = left atrium *LPV* = left pulmonary vein *RPV* = right pulmonary vein *Sept I* = septum primum (From Van Praagh R and Corsini I Am Heart J 78 379 1969)

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leaders such as principals and department heads in the high schools It may be extremely helpful to work with people skilled in public relations and reach the general public with newspaper notices Special groups such as clubs and organizations may be contacted directly Ultimately people become interested by word of mouth and seek instruction

In summary the mechanics of initiating a program of widespread community training in CPR have been described It is possible to successfully accomplish such a program with motivated volunteer personnel

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Training format

The instruction is given either in four successive hours on one day, or four one hour sessions on four successive days. The material presented is in accord with the J A M A supplement on cardiopulmonary resuscitation.[14] The program content is divided into four parts

1. Introduction and film
2. Slides and discussion
3. Manikin demonstration, practice and proficiency evaluation
4. Testing and discussion

1 The introductory material presented may vary depending on the audience, but basically it serves to establish an instructor–student relationship. It usually points out the importance of maintaining cardiopulmonary functions to prevent irreversible brain damage. The film presentation used is "Pulse of Life"[17] which is both instructive and motivational. It demonstrates the steps in establishing an airway, restoring breathing and maintaining circulation as well as depicting the actual use of CPR in real life situations.

2 The slides used are the American Heart Association slides on basic CPR[18] and the presentation is supplemented by the American Heart Association pamphlet on the CPR slides[19] which is given to each student. Questions and discussion are encouraged.

3 In the manikin practice session, the student is able to practice and apply the techniques described in the previous sessions. The principal instructor demonstrates the proper techniques of artificial ventilation and artificial circulation for a single rescuer and for two rescuers. The proper compression–ventilation ratios are emphasized, the pitfalls in performance of CPR, precordial thump and special resuscitations (e g, drowning) are discussed. The students are separated into small groups. Each group works with an instructor on the manikin. In addition to the adult sized manikin an infant manikin is also used. We have found it extremely helpful to incorporate the previously trained Fire Department and other rescue personnel to help with the manikin practice. Usually four or five instructors assist the principal instructor thereby enabling us to obtain a one to one teaching relationship with each student. Manikins used are specifically designed for monitoring the student's effectiveness in maintaining proper ventilation and cardiac compression. The instructors carefully observe that the students follow the proper techniques to obtain an open airway, restore breathing and maintain circulation. Instructors pay special attention to the very important details of head tilt, mouth and nose seal, adequate ventilation, location and detection of carotid pulse, hand position, and the mechanics of sternal depression. After the students have practiced in teams of two and as a sole rescuer, they are tested for their proficiency.

A written examination is the last phase of instruction. It serves to reinforce the material presented and reemphasize the important points. Papers are then exchanged among the students and corrected orally. During the discussion, any misconceptions and omissions can be worked out. This phase of the program is exceedingly important as it enables the instructor to assess the student's comprehension. Students who successfully complete the course are given a wallet size card from the Heart Association certifying completion of the basic CPR course.

Benefits of the CPR training program

There are numerous benefits of such a training program in addition to developing a population proficient in CPR. The participants in the course of discussion become aware of the early warning signs of a heart attack and familiar with the management of related emergency problems. They also develop insight into the total emergency medical system of the community. They recognize that emergency services cannot operate in a vacuum but become more effective when the specialized knowledge of basic CPR is disseminated to the general public. The trainees in turn can exert their influence to upgrade existing systems, or speed the development of an emergency care system in their community. Those who are motivated may ultimately seek further training to become instructors and teach others.

The keys to a successful CPR training program are in several areas. Initially, an active planning group has to form to guide the bringing of CPR to the general public. Joint sponsorship such as Red Cross and Heart Association facilitates the development of the program. Secondly, the format of instruction must be implemented by skilled and highly motivated instructors. Finally, various segments of the community must be reached. The latter goal may be accomplished in several ways. Contacts should be made with educational

Fig 1 Inotropic response of the isolated cat papillary muscle to MDF The developed tension of isometric contractions is indicated on the ordinate and tracing speed on the abscissa At arrows Krebs-Henseleit solution was exchanged for MDF sample (vice versa) A depressant activity of 60 MDF units occurred Of note is recovery to the base-line contractility after washout of the test sample with Krebs Henseleit solution.

cardiac performance seen in the course of many forms of shock However there has been a paucity of studies on MDF in cardiogenic shock

We undertook the following study The experimental shock model was produced in dogs by embolization of left coronary artery with metallic mercury One group of 12 dogs with developed cardiogenic shock were allowed to proceed on their natural course In another group of 8 dogs which also met the criteria for occurrence of cardiogenic shock a pharmacologic dose of glucocorticoids (methylpredonisolone Solu Medrol 30 mg per kilogram of body weight Upjohn) was administered intravenously at the time of coronary embolization. Blood samples were drawn at intervals before and after the embolization and processed quantitatively for MDF MDF was isolated from plasma ultrafiltrates on Bio gel P2 column chromatography eluted with Krebs Henseleit solution The activity of MDF was assayed using isolated cat papillary muscles and expressed as MDF units (1 unit = 1 per cent decrease in developed tension) MDF exerted a prominent negative inotropic effect on isometric contractions of the papillary muscle under standard conditions (Fig 1) The experimental variables such as the electrolyte concentrations pH osmolarity oxygenation and temperature were carefully controlled to exclude unrelated inotropic responses For electron microscopic cyto hemical examinations of pancreatic lysosomes biopsies were taken from representative dogs five hours after coronary embolization

We found that MDF isolated from cardiogenic shock was dialyzable filterable through a synthetic membrane with an appropriate pore size soluble in aqueous media heat stable up to 80 C and recovered in the chromatographic peptide peak of molecular weight range between 800 to 1 000 It gave a positive ninhydrin test and was inactivated after enzymatic destruction with a nonspecific protease (pronase) We found the amino acid residues common with MDF after acid hydrolysis were limited to alanine aspartic acid glutamic acid glycine iso leucine leucine serine threonine and valine Our findings are in agreement with the reported results and indicate that MDF is in fact small peptides

In our group of nontreated dogs there occurred marked increases in plasma activity of MDF as cardiogenic shock progressed. The time course study showed that the activity of

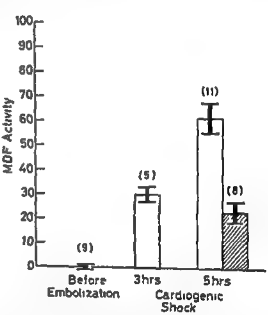

Fig 2 MDF activity in cardiogenic shock. Heights of bars are mean values brackets indicate S E M and numbers in parentheses indicate numbers of MDF samples assayed As cardiogenic shock progressed MDF activities of the nontreated group increased markedly (blank bars P < 0 001) above pre embolization values MDF activities of the methylprednisolone-treated group were significantly lower (hatched bars P < 0 001) than in the nontreated group The control samples obtained before coronary embolization contained *no appreciable* MDF activities.

MDF reached 30 ± 3 2 units and 61 ± 5 units three and five hours after coronary embolization respectively The plasma rises in MDF activity appeared to be inversely related to hemodynamic deterioration of the animals which *maintained* in persistent hypotension and low cardiac output eventually dying four to nine hours after induction of *cardiogenic shock* In other types of shock, it has been demonstrated that protease inhibitor (Trasylol) is effective in *prevention of* MDF formation probably by inhibiting the activation of pancreatic

Annotations

Aspirin and myocardial infarction

Acetyl salicylic acid (aspirin) has a marked and prolonged inhibitory effect on platelet aggregation.[1,2] Aggregation to collagen is abolished, as is the secondary wave of aggregation to adenosine diphosphate (ADP). This latter probably represents the release of endogenous ADP from the platelets themselves and when it occurs aggregation is irreversible.

Platelets are believed to play a key role in thrombosis. There is therefore a growing interest in aspirin and other drugs with an effect on aggregation as possible preventive measures in thromboembolic conditions.

Two relevant reports have recently been published. One gives the results of two large independent observational studies involving a combined total of 776 patients discharged from hospital following acute myocardial infarction and 13,809 control patients with other diagnoses. There was evidence of a marked negative association between regular aspirin intake prior to admission and nonfatal infarction. The reduction in aspirin takers among the infarction patients was consistent with at least a fifty per cent protection by regular aspirin consumption. The other report is of a randomized controlled trial of a single daily dose of aspirin (300 mg.) given to half of a group of 1,239 men who had had a recent myocardial infarction. The results show a reduction in secondary mortality of 25 per cent at twelve months after admission to the trial. This effect is statistically inconclusive at $P < 0.05$.

While proof is still lacking, the results of the published studies are most suggestive that a beneficial effect of aspirin is present. There is therefore an urgent need for further data. Work is continuing in Wales and similar trials are in progress in the United States and in Germany. Results will be awaited with great interest.

If the results establish that aspirin is beneficial in preventing myocardial infarction, one may infer that tests of platelet aggregation as measured by Borne or similar techniques would be of direct relevance to cardiovascular morbidity and mortality. Risk factors may then be evaluated more directly in relation to a single mechanism. This will avoid the confounding of several mechanisms which are probably involved in conventional epidemiologic techniques as used in the Framingham and similar longitudinal studies.

In addition, one may be in a position to evaluate the concepts of cardiovascular disease which have been derived from the thrombogenic views of Rokitansky[6] that the atherosclerotic process is initiated by aggregates of platelets and fibrin laid down on the intima. Thus, the next generation of pathologists could learn whether or not anti-aggregant drugs are also anti-atherosclerotic.

H. Jick
Boston University Medical Center
Boston Collaborative Drug Surveillance Program
Waltham, Mass.
P. C. Elwood
M. R. C. Epidemiology Unit
Cardiff, Great Britain

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Myocardial depressant factor in cardiogenic shock

A myocardial depressant factor (MDF) was discovered 1966 in the plasma of cats in postoligemic shock. Since that time extensive studies have been carried out by Lefer and co-workers for validation of MDF as a shock factor. MDF has been found to occur in several mammalian species including cats, dogs, baboons, and man during a variety of types of circulatory shock. Thus, it is not restricted to a single species or shock entity. MDF has been partially characterized. It has a molecular weight of 800 to 1,000 and appears to be a peptide or related substance (i.e., a glycopeptide). The reported evidence has indicated that the major site of MDF production is the ischemic pancreas, in which acid proteases of lysosomal origin catalize the degradation of endogenous substrate protein to form MDF. MDF has been shown to exert as its primary action a prominent negative inotropic effect on the isolated papillary muscle, isolated perfused heart, and the in situ heart and, moreover, to be capable of inducing shock states by diminishing cardiac output when injected intravenously in intact animals. It is this adverse potency of MDF on myocardial contractility that is implicated in deterioration of

These are those countries in which in fact there has been the greatest progress in both radiodiagnostics and radiotherapy In other countries the situation has not developed in this direction or it is developing very slowly one country that fits the latter description is Italy

Our country which several decades ago was the first to introduce into the university curriculum the teaching of Radiology as an obligatory subject has always had a tradition of a very high standard in the field of radiodiagnostics. But it is perhaps the strength and tradition of the "unitary university teaching of radiology that has delayed an adequate development of radiotherapy

In Italy today there are radiotherapy departments in some hospitals, but in the majority of institutions and in universities always, radiodiagnosis and therapy are practiced and what is worse taught by the same person The official title of the university teaching is that of Radiology" Today however this is a concept which is outworn if the professor divides his time between diagnostics and therapy it is difficult for him to be up-to-date in both Should he dedicate himself mostly to one of the two he is bound to neglect the other and this inevitably influences the direction the activity of his institution

It is maintained by some that for the teaching of students a general knowledge would suffice I challenge this because at the university level the teaching should be sustained not only by experience and by being always up-to-date but also by a real enthusiasm or better still, by a deep passion for one's own subject. I challenge it again most emphatically because in Italy the postgraduate teaching which should build the echelons of specialists is imparted under the same conditions. To date we have reached the stage of having established two diplomas of specialist—one in Radiodiagnostics" and one in Radiology" which comprises also radiotherapy But even in the latter case very often the training of the specialists is chiefly in diagnostics. Not even the opportunity to reach the standards which will be necessary for a free movement of labor in the field of the European Economic Community has had any practical effect

Although the workings of Italian bureaucracy are extremely slow[4] and limit considerably the possibility of modifying the form of teaching I maintain that it is undoubtedly the traditional attitude of the majority of university professors of radiology which puts obstacles in the way of real progress

With some exceptions we see the result of this state of affairs in the situation of radiotherapy in Italy in its practice in research and in the ancillary position it still has when compared to surgery and gynecology

In my view this undesirable state of affairs for Italy and for other countries in a similar situation is encouraged by the equivocal words, "Unity of Radiology" on the Statute of the European Society of Radiology which is underwritten by the representatives of countries where radiology may be perhaps united in respect of its social and administrative aspects, but is certainly not so in its practice in research, or in teaching

Unity of Radiology" is perhaps a useful "political" compromise but in a stagnant situation it represents a dangerous support to our status quo

Do the representatives in the European Association of Radiology of those countries in which separation has already been achieved realize that they may be acting unwittingly as a cover for what they implicitly regard as an underdeveloped and not-developing situation, and that every endeavor should be made to clarify the interpretation of the meaning of "Unity of Radiology"?

In the last few months I put this question in a Letter to the Editors of *The Lancet* and the *British Journal of Radiology* because British colleagues are properly proud of the success of the longstanding separation of the two main branches in their country But I think that the problem may be interesting also for American colleagues

Giulio De Giuli M.D
Professor of Radiology
University of Florence
Florence Italy

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Of the P-R segment depression and atrial infarction

Acute myocardial infarction of the left ventricle is often associated with a P R segment depression of a fraction of a millimeter or more (Fig 1) In a routine study of all hearts of patients autopsied at the New Orleans Veterans Administration Hospital since the hospital opened in 1945 such a P R segment depression was always associated with infarction of an atrium The tracing shown in Fig 1 is an example of this phenomenon. Such P R segment depression is not a routine change associated with all acute left ventricular myocardial infarcts, but is a fairly common occurrence When the P R segment is depressed, the left ventricular infarct is usually large and basal in location i e an infarct which extends to and above the A V groove The area of atrial infarction is usually located near the A V groove As would be expected in the thin walled atria the lesion is transmural Such a P R segment depression sometimes occurs during episodes of

proteases also alpha adrenergic blockers by maintaining adequate splanchnic blood flow to the pancreas and glucocorticoids by circulatory effect as well as by stabilizing lysosomal membranes By far the most successful pharmacologic agents in prevention of MDF formation are the glucocorticoids (hydrocortisone and methylprednisolone) In our group of methylprednisolone treated dogs there was a significant degree of suppression on the plasma rises in MDF activity reaching only 23 ± 4 2 units five hours after coronary embolization (Fig 2) All dogs with these massive doses of glucocorticoids survived longer than the nontreated dogs exhibiting early and gradual improvement in aortic blood pressure and cardiac output

Our correlative electron microscopic cytochemical examinations of the pancreas of the nontreated dogs revealed striking alterations of the lysosomes indicative of their increased fragility and autophagic activity accompanied by severe ischemic cellular injuries which seemed to be associated with the plasma rises in MDF activity On the other hand we observed a slight to moderate degree of ischemic cellular injuries with remarkable preservation of lysosomal integrity in the pancreas of the methylprednisolone treated dogs

In the present study we confirmed the previous work on MDF and extended it in cardiogenic shock The data presented suggest that MDF may be an important determinant in impairment of the myocardial performance later in the course of shock presumably affecting contractility of the noninfarcted portion of the heart muscle However among many other shock factors and in a situation as complex as that which exists in cardiogenic shock to what extent this cardiotoxic substance contributes to development of refractory pump failure and lethality of shock cannot be determined Our data with glucocorticoids indicate that one possible mechanism by which these massive doses exert the beneficial effect in cardiogenic shock is in addition to an action on the cardiovascular system stabilization of the lysosomes of planchnic tissues particularly the pancreas thus preventing formation and plasma accumulation of MDF

Kiyoshi Hosono MD
Minoru Okuda MD
Department of Medicine
Defense Medical College
Iruma City Japan

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Radiology

The applications in the field of medicine of the discovery of W C Roentgen were very rapid and fortunate because many doctors grasped its importance and also because the apparatus used was easily adaptable in the physics laboratories The medical men who first dedicated themselves to this activity were supported by their medical non specialized training and learning mostly technical details of the apparatus they were using began to discover medical radiology day by day

It is natural that in these conditions the same people used x rays for diagnostic and therapeutic purposes With radiology becoming more advanced it became clear that the mass of knowledge had become too large to be managed by one person A differentiation into two activities began to take place

Radiodiagnostics is a type of semeiotics which requires of a medical man the acquisition of a specialized knowledge of methods and techniques of investigation and a revision in terms of radiodiagnostics of all his previous training

Radiotherapy on the other hand is a clinical branch on the same level as internal medicine and surgery

Though knowledge of radiological anatomy and of technical possibilities of radiodiagnostics is certainly useful to the radiotherapist (localization of lesions laying out of treatment plans) he does not need to know about examination methodology and the semeiotics of the different morbid conditions This however is unavoidable for the radiodiagnostician and is today so diversified as to give rise to actual subspecializations such as neuroradiology pediatric radiology etc

In different countries the adaptation in practice and teaching to this state of affairs has taken place in different ways Paris Stockholm and many British centers were the first to identify radiotherapy as a distinct discipline they were followed in their own countries and also abroad by other Scandinavian countries some British Commonwealth countries the Netherlands and United States etc

Letters to the Editor

Bacterial endocarditis in IHSS

To the Editor

In Wang Gobel and Gleason s interesting article ' Bacterial endocarditis in idiopathic hypertrophic subaortic stenosis" (AM HEART J 89 3 9 36ɔ 19"ɔ) the antimicrobial therapy for enterococcal endocarditis described in the case report was less than optimal The patient received intravenous aqueous penicillin alone for 10 days followed by intravenous lincomycin alone for 7 days followed by the combination of intravenous cephalothin and intramuscular streptomycin

The recommended treatment for enterococcal endocarditis is intravenous aqueous penicillin and intramuscular streptomycin This combination shows a synergistic bactericidal effect in vitro and therapy with these agents has given the best results If penicillin allergy d velops as occurred on the tenth day in this patient vancomycin should be substituted rather than a bacteriostatic drug like lincomycin Vancomycin also acts synergi tically in vitro with streptomycin against the enterococcus Enterococci are relatively resistant to cephalothin in vitro and treatment with this drug either alone or in combination with streptomycin has not been successful Cephalothin is also a poor choice in a patient with bacteremia because it doesn t penetrate the blood brain barrier well It should be noted that the patient died from the rupture of a presumed mycotic aneurysm of the middle cerebral artery while on cephalothin

In summary treatment for enterococcal endocarditis is penicillin and streptomycin or vancomycin and streptomycin If the patient had received this optimal antimicrobial therapy the aortic valve perforation on day 17 and the ruptured mycotic aneurysm on day 64 might have been prevented

Richard F Katholi M.D
Peter M Levitin M D
Department of Medicine
University of Virginia Hospital
Charlottesville Va 22901

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Reply

To the Editor

We wish to thank Drs Katholi and Levitin for their comments We have referred their letter to Dr Horace Zinneman, of our Infectious Disease Section who participated in the care of this patient In general we agree with their

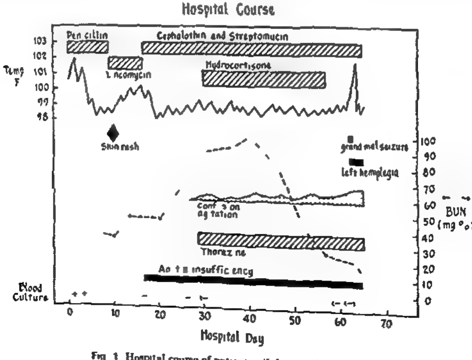

Fig 1 Hospital course of patient with bacterial endocarditis

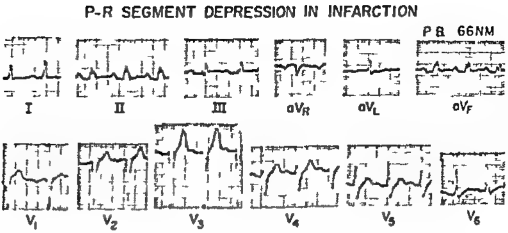

Fig 1 P R segment depression in acute myocardial infarction

angina pectoris but disappears when the anginal episode subsides whereas with myocardial infarction the P R segment slowly returns to the isopotential level as the acute infarct heals In rare instances the P R segment never returns to the isopotential level In essence the P R segment tends to shift with atrial infarction and behave as the S T segment does with ventricular infarction except that it shifts less frequently and rarely elevates during myocardial infarction.

G E Burch M D
Tulane University School of Medicine
and Charity Hospital
New Orleans La

the portion of the graft which remains patent and then the flow is directed into the territory of the anterior descending artery. It is obvious that direct measurements of the flow were not done simply because this is not feasible in a patient. Of course if the chest were opened, this steal syndrome could be validated by temporary occlusion of the graft and by measurements of the distal flow in the territory of the circumflex artery from where the blood is being diverted by this partially opened surgically created communication. The fact that the distal circumflex artery was perfused is clearly demonstrated when comparison is made between the angiogram presented in our paper and that of the preoperative catheterization. There is no progression of the disease in that portion of the circumflex artery. If no further progression of the disease was demonstrated between the two coronary arteriograms in the distal circumflex artery and the flow in the second study appears to be decreased, this tends to strengthen the argument that a steal phenomenon is occurring. Of course we realize that absolute proof for diversion of flow from one territory to another could not be made beyond any doubt.

I would not use the subjective improvement of the patient as an argument against the steal phenomenon since multiple other factors may influence the course of angina pectoris, as is clearly known to physicians who follow patients with angina pectoris for extended periods of time.

We recently had the opportunity to study another patient in whom one graft had been constructed to the anterior descending artery and another to a lateral ventricular branch. The anterior descending graft was placed before the obstruction rather than distal to it. This patient demonstrated a phenomenon which could also be called a steal syndrome, namely, flow occurred between the proximal anterior descending artery and the graft and back to the aorta. The flow in this case was being diverted from the anterior descending proximal portion around into a patent graft and into the aorta during parts of the cardiac cycle. This patient demonstrated electrocardiographic changes of ischemia of the anteroapical region.

We feel that the steal syndrome is possible within the coronary circulation but is usually induced by a surgical intervention and is quite rare.

Benjamin Befeler, M.D.
Associate Professor of Medicine
Chief, Cardiovascular Laboratory
University of Miami School of Medicine
Veterans Administration Hospital
Miami, Fla. 33125

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Massive pulmonary embolism: The role of pulmonary embolectomy

To the Editor:

In the April issue of the JOURNAL (AM HEART J 89:413, 1975) Alpert and associates question the role of pulmonary embolectomy in the treatment of massive pulmonary embolism. Such questioning is not new and has led to increasingly precise definition of the ways in which differing categories of patients with pulmonary embolism are best treated. However, to imply that pulmonary embolectomy is of little value in the treatment of this disease is to deny a life saving procedure to a significant, though admittedly small number of patients. In the same issue Beall and Collins have defined one group of patients in whom embolectomy is life saving, namely those in whom survival beyond one hour would be inconceivable without the immediate institution of partial cardiopulmonary bypass followed by embolectomy. We would like to draw attention to another group of patients in whom embolectomy is life-saving—those who have survived for several hours but will still die unless the hemodynamic disturbance can be reversed more rapidly than is possible with thrombolytic therapy and certainly more rapidly than occurs with anticoagulant therapy. Such patients have been identified by Tibbutt and associates. They are patients in shock with angiographically "super massive" embolism. Among the 30 patients with life threatening embolism reported by Tibbutt and associates there were seven in this category. Of these one died of a recurrent embolus after 18 hours of heparin treatment (and was the only death in the series), but five deteriorated so rapidly that the clinician in charge elected to withdraw the patients from the trial so that alternative therapy could be instituted. In four of these patients and one other with angiographically slightly less severe pulmonary embolism, emergency pulmonary embolectomy was then performed successfully in every case. (The final patient was changed from heparin to streptokinase.) Admittedly none of these patients had preexisting cardiorespiratory disease—but neither did they have metastatic carcinoma or other terminal disease—and all are alive three to four years later. Thus in our experience embolectomy can be life saving and may be needed even in patients who have survived long enough for transfer to a special center for diagnosis and consideration of embolectomy. Nor is it true, as stated by Alpert and associates, that "the majority of patients who undergo embolectomy do not survive." From 1964 to 1971 we performed emergency embolectomy on 31 patients with isolated acute massive pulmonary embolism with an over all immediate mortality rate of 23 per cent. From 1968 the only patient who died was having external massage prior to embolectomy and would undoubtedly have been better managed with partial bypass in the first place, as suggested by Beall and Collins. In this highest risk group—patients who have already suffered a circulatory arrest—the high mortality rate of 66 per cent would probably have been reduced by adoption of this technique.

We agree with Alpert and associates that chronic cor pulmonale is an extremely rare complication among patients who survive massive pulmonary embolism; the problem is to obtain the largest possible number of survivors and this will only be achieved by selecting the treatment appropriate to the patient's status. In those who will not survive more than a few minutes it is partial bypass followed by embolectomy. In those who survive two hours or more it may be thrombolytic or heparin therapy depending on the severity of the hemodynamic disturbance and the urgency of the need to reverse this disturbance. In a small number the correct treatment is emergency pulmonary embolectomy on cardiopulmonary bypass—and the candidates for this form of treatment are certainly seen several hours after the onset of embolism. Embolectomy can be performed at low risk and is well

statements regarding guidelines for therapy of enterococcal endocarditis Streptomycin was not combined with penicillin therapy initially because the bacteria were very sensitive to penicillin as judged by serum minimum bactericidal concentration (MBC) of 1 80 The organism was sensitive to penicillin lincomycin and cephalothin all at an MBC of less than 0 125 mg/ml The patient was dramatically improved following penicillin therapy

In retrospect perhaps a different antibiotic could have been substituted when hypersensitivity to penicillin developed as suggested by deterioration in the clinical course during lincomycin therapy

The combination of cephalothin and streptomycin resulted in a serum MBC of 1 320 With this therapy the patient improved and blood cultures failed to grow bacteria In retrospect the sensitivity to lincomycin strongly suggests that the endocarditis was due to an infection with *Streptococcus bovis* a very sensitive Group D streptococcus which does not grow in 6 5 per cent NaCl or *Streptococcus faecalis* medium Its eradication by the described therapy in 1971 would lead one to suspect that we were dealing with *Streptococcus bovis* Today the sensitivity to lincomycin is one of the screening tests employed in our laboratory to distinguish *Streptococcus bovis* from enterococcus

At autopsy cultures of the blood cerebrospinal fluid and aortic valve failed to grow organisms Histologic sections failed to reveal active infection in any organ Specifically there was no evidence of meningitis The site of bleeding was not specifically located but since it was most likely an arterial lesion it would not have been influenced by the ability of an antibiotic to cross the blood brain barrier The aortic valve was not perforated (Fig 6 page 363) and aortic insufficiency most likely represented deformation of the aortic valve secondary to vegetative lesions and organizing valvulitis Therefore no site of active infection was discovered at autopsy

We believe that the prolonged illness prior to initiation of antibiotic therapy and the immunologic manifestations of bacterial endocarditis and not uncontrolled infection contributed to the death of this patient as discussed and referenced on page 364 of the paper We include a graphical presentation of the hospital course (Fig 1) of this patient

Fred L Cobel M D
Kyuhyun Wang M D
Horace Zinneman M D
Veterans Administration Hospital
54th St and 48th Ave South
Minneapolis Minn 55417

Inter coronary steal syndrome

To the Editor

First of all I would like to thank Dr Befeler and colleagues for sending me a reprint of their article which appeared in your JOURNAL, probably as a response to my challenging letter that appeared in *The American Journal of Cardiology* I would like to make some comments in response to their case presentation and discussion They have still not proved to me any steal phenomenon in the coronary arteries In their Fig 1 when they injected into the left coronary artery we see simultaneous filling of both the left circumflex branch and the inverted V limbs of the graft filling the left anterior descending coronary artery—i e the left circumflex branch beyond the anastomosis of the vein graft is being filled simultaneously in almost all the frames when the graft is filled Besides I don t see any block in the obtuse marginal branch as they tried to depict in their diagram (their Fig 4) Furthermore they have not shown angiographically any channels between the distal portion of the circumflex coronary artery and the vein graft I do agree with their interpretation of closure of straight limb of Y graft Whatever might be the cause of closure of the graft, I feel jump grafts, "snake grafts and Y grafts should be avoided As a result of closure the inverted "V" portion of the graft is acting as a long conduit carrying blood from the normal circumflex coronary artery to the diseased left anterior descending

As the authors know one of the accepted modes of treatment of subclavian steal syndrome is a bypass graft between normal common carotid and the subclavian artery so is the principle of crossover femoro femoral artery graft in unilateral diseased iliac arteries In these situations angiograms show simultaneous filling of the carotid system and the subclavian arteries That does not mean there is decrease in the flow of blood in the carotid system beyond the graft or the femoral system in the donor distal leg There is ample evidence of measurement of the flow of blood to attest to the above fact Of course I do know it would be hard to prove the same observation in coronary artery system In this case I feel simply that the end result is that the left anterior descending coronary artery is being filled by a long graft from the circumflex coronary artery—i e there is no steal phenomenon merely filling of L.A D coronary artery system by a graft Besides, this patient shows objective and subjective improvement which the authors like to credit only to the patent right coronary graft Hence I feel inter coronary artery steal syndrome is purely hypothetical

Gopal Rao M D
Department of Thoracic & Cardiovascular Surgery
Shadyside Hospital
Pittsburgh Pa 15232

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Reply

To the Editor

We thank Doctor Rao for his letter referring to our paper Inter coronary steal syndrome resulting from aortocoronary bypass surgery published in a recent issue of the AMERICAN HEART JOURNAL.

Our report portrays a situation where the territory supplied by the distal circumflex artery shows decreased flow angiographically at the time that the flow is diverted into the open portion of a Y graft which in turn fills the distal anterior descending artery We feel satisfied that the criteria for a so called steal syndrome are present in our case The blood supply to the inferolateral wall of the left ventricle supplied by the circumflex artery and its branches is being diverted into

Book reviews

Stress Testing Principles and Practice By Myrvin H Ellestad, M D Philadelphia 1975 F A Davis Company 296 pages.

This publication comes at a time of great interest in treadmill exercise testing of cardiac function throughout the U.S.A Ellestad has had considerable experience with the procedures of stress testing The apparatus methods and interpretation of data are clearly described However stress testing has not only its limitations but it is potentially hazardous. If the procedure were not hazardous, there would be no need for standby drugs defibrillators well trained nurses and doctors Those precautions are necessary and reflect the dangers of the procedures Even the Master s two-step test is not without risk to the patient with heart disease The physician must consider seriously the extent of liberties he has with his patients lives The interpretation of records are difficult for example in regard to the magnitude of ST segment depression which is abnormal.

In spite of such problems, the interest in stress exercise *testing is constantly increasing* The use of stress testing is well described in this publication for those who are using the procedure or who plan to enter the program of stress exercise Nevertheless, this reviewer advises the readers to read the book critically and cautiously especially with regard to some statements which could be challenged Treadmill stress testing is a new diagnostic procedure which cannot replace clinical bedside cardiology Its value indications for use and interpretation of recordings as advocated by Dr Ellestad are clearly indicated in his book

The Conduction of the Cardiac Impulse By Paul F Cranefield M D Ph.D Mount Kisco N Y 1975 Futura Publishing Company 404 pages

Cranefield has written an excellent book on an important aspect of cardiology That he is an expert on the subject is well recognized by all who work in the field of cardiology The discussions are concerned with fundamental principles of impulse transmission in the heart principles important in clinical practice Physicians must know the physiology of conduction of impulses in the heart in order to manage cardiac arrhythmias logically The principles in electrophysiology presented in this book are of practical nature and form the background for understanding drug action and clinical manifestations of disturbances in cardiac rhythm The book is highly recommended

Cardiovascular Physiology Edited by James V Warren M D Stroudsburg Pa 19 5 Halsted Press 441 pages.

Dr Warren has gathered several publications that he considers of historic importance in cardiology This is acceptable and reflects his own opinion However others have their ideas of what was important Omissions can cause great difficulties. For example Sir Thomas Lewis contributions to clinical and experimental electrocardiography were outstanding, but only one publication was included in the book The role of anatomists and electron microscopists such as Huxley Keith, and Flack, who provided the fundamental background for physiologic studies are not included. The original experiments of *Stephen Hales*, A N Richard, Withering and many others are also not included The reader will find this book interesting in large part for the subjects and people selected *Warren* attempted to limit publications related to man himself which decidedly influenced the selection of papers included

Diagnostic Methods in Cardiology Edited by Nobel O Fowler M D Philadelphia 19 5 F A Davis Company 455 pages

This issue of *Cardiovascular Clinics* reviews methods in diagnosis in cardiology Like previous issues, it is designed for the practicing physician Gallop rhythm auscultation in general, arterial and venous wave forms exercise electrocardiography computer analysis of the electrocardiogram ambulatory monitoring of the arrhythmias His bundle recordings and vectorcardiography are among the many subjects discussed The contributors in their respective subjects attempted to indicate the practical aspects of the problems. Those in a busy practice should study the various chapters of the book carefully For example the chapter on coronary *angiography is summarized* to indicate its usefulness in clinical practice but the hazardous nature of the procedure indicated by the tables is not adequately emphasized Where some laboratories report a mortality rate of over 2 per cent the author fails to be convincing that such a diagnostic procedure is worth the risk Then the operative risk must be added to those who survive the diagnostic procedure itself Some of the diagnostic procedures are expensive for the information derived e g vectorcardiography Regardless the reader will find a great deal of interesting information in this publication and the opinions of the respective contributors is evident from their discussions.

The Physiology of Physical Stress A Selective Bibliography By Carleton B Chapman M D and Elinor C Reinmiller Cambridge Mass 1975 Harvard University Press 369 pages.

The title of this publication adequately describes its contents. The value of this book is certainly challenged by the tremendous bibliographic services offered by the National Library of Medicine and its various ancillary services Physiologists and cardiologists with special interest in physical stress will find this book useful The book should interest at least some people particularly in that the bibliography does indicate to contemporary investigators that much of the work done today was already done very well many years ago

New Horizons in Cardiovascular Practice Edited by Henry I Russek, M D., Baltimore 19 5 University Park Press 5?1 pages. Price $34.50

This publication of the papers presented at the symposium on cardiovascular practice held in New York City during December 1973 is as usual a valuable collection This annual symposium conducted by Dr Russek is one of the outstanding meetings held in the U S A in the field of cardiology The contributors are leaders in cardiology and the subjects discussed include the most important problems of the year This publication consists of presentations on bedside management of cardiovascular diseases advances in diagnostic methods ischemic heart disease *medical* and surgical management of angina pectoris and myocardial infarction management of hypertension disorders of cardiac rhythm microcirculatory disease and others This book is highly recommended as a source *of review* of these many clinical problems for those who were unable to attend the sessions

worthwhile since the patients are certainly not all suffering from terminal disease—they are frequently fit young adults convalescing from routine surgery or from childbirth

M Paneth F R C.S
G.A H Miller D M F R C P
Brompton Hospital
Fulham Road
London SW3 6HP
England

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Reply

To the Editor

We thank Drs Paneth and Miller for their comments and hope that the following will clarify our position The purpose of our paper was not as stated by Drs Paneth and Miller to encourage physicians to deny a life saving procedure to a significant though admittedly small number of patients Indeed our article states that pulmonary embolectomy should be reserved for the exceptional circumstance of persistent hypotension in a patient with documented massive pulmonary embolism whose overall status is such that pulmonary embolectomy is clinically appropriate "

In the reference cited by Paneth and Miller i e Tibbutt and associates[1] the seven patients with super massive embolism all demonstrated persistent refractory hypotension and thus would also have been candidates for embolectomy at the Peter Bent Brigham Hospital That such patients are rare is documented by the fact that we saw only one such individual during a 10-year period

Our major point is that patients with massive embolism who remain normotensive or whose hypotension is responsive to vasopressors usually survive with prophylactic therapy (venous interruption or vigorous anticoagulation) As noted in our article[2] 81 per cent of patients in the above mentioned category survived with prophylactic therapy alone and were discharged from the hospital This compares favorably with 77 per cent survival following embolectomy as cited by Paneth and Miller[3]

We believe that the most important problem facing physicians who deal with pulmonary embolism is not how to set up partial cardiopulmonary bypass machines in the emergency room but rather how to diagnose the many cases of pulmonary embolism which go undiscovered and hence untreated Two hundred thousand Americans die each year as a result of pulmonary embolism and in most of these the diagnosis is not even suspected

More can be done to reduce this mortality rate through physician awareness of the myriad clinical presentations of pulmonary embolism than can be accomplished with expensive and infrequently employed partial bypass machines and embolectomy procedures

Joseph S Alpert M.D
James E Dalen MD
Dept of Cardiovascular Medicine
University of Massachusetts Medical Center
Worcester Mass 01605

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Announcements

Symposium on cor pulmonale chronicum

The first common international congress of the European Society of Cardiology and the European Society of Physiology of Respiration will feature a symposium entitled "Cor pulmonale chronicum" to be held in Munich on March 4 through 6 1976 The program will cover the definition epidemiology pathology and pathophysiology of cor pulmonale chronicum. Clinical presentations will include clinical course diagnosis, therapy prognosis and prevention

For registration and other information contact PD Dr S Daum, I Medizinische Klinik and Poliklinik der Technischen Universität 8000 Munich 80 Ismaninger Str 22 Telephone (089) 4140-2353

Symposium on pediatric cardiology

The Johns Hopkins University is sponsoring the Helen B Taussig International Symposium on Pediatric Cardiology May 24 through 26, 1976 at the Johns Hopkins Medical Institutions, Baltimore Maryland The Symposium is endorsed by the American Academy of Pediatrics and the Committee on Cardiovascular Disease in the Young of the American Heart Association Tuition is $150 00 and the program qualifies as an approved course in Continuing Medical Education enabling physicians who attend to qualify for 24 credit hours (in Category I) towards the Physicians Recognition Award of the American Medical Association

The ten major sessions will consider Tetralogy of Fallot Rheumatic Heart Disease Hypertension and Hyperlipidemia in the Young The Sick Infant Advances in Medical Management The Sick Infant Advances in Surgical Techniques The Sick Infant Problems After Surgery Society and the Child with Cardiovascular Disease Cardiomyopathies The International Scene Cardiomyopathies N w Approaches to Diagnosis and Therapy and Etiology of Congenital Heart Disease

For further information contact Glenn C Rosenquist M.D Symposium Director CMSC 274 The Johns Hopkins Hospital, Baltimore Maryland 21205 Call (301) 955-3611

Exercise testing in clinical practice

The University of Texas Health Science Center at Houston Division of Continuing Education and Medical School, announce a program *Exercise Testing in Clinical Practice* to be held March 5 19 6 at The University of Texas Medical School Auditorium Houston Texas. Co sponsor–Baylor College of Medicine

The effects of exercise on the cardiovascular system are important in the diagnosis and the assessment of cardiovascular function in patients with heart disease In this course particular emphasis is placed on the diagnosis and management of coronary heart disease The significance of electrocardiographic changes, including cardiac arrhythmias is discussed. Other topics are the effects of exercise on coronary risk factors and in the evaluation of patients following coronary bypass surgery The value of exercise in the post infarction patient and the effects of exercise on coronary blood flow are included. The cardiovascular response to the ordinary social smoking habit and the relation of orthostatic tolerance to cardiovascular stress are discussed

For further information contact The Office of the Director The University of Texas Health Science Center Division of Continuing Education P O Box 20367 Houston Texas 77025 Call (713) 792-4671

Current problems in intensive care

The Department of Anesthesia in cooperation with Extended Programs in Medical Education University of California School of Medicine San Francisco California is sponsoring a postgraduate course "Current Problems in Intensive Care–Pulmonary Care" This course is designed to cover both theoretical and practical aspects of the causes, diagnosis and treatment of pulmonary edema. The course will be held in the Colonial Room of the St Francis Hotel Union Square San Francisco California on April 1 and 2 1976 fee $100 00 The program is acceptable for 9 hours *Category I credit* toward the Certificate n Continuing Education for the California Medical Association and The American Medical Association

For Registration information contact Extended Programs in Medical Education Room C-135G University of California San Francisco CA 94143 Phone (415) 666-2483 or 666-2894 For program information call (415) 666-4251

Cardiac conference

The Colorado Heart Association presents the High Country Cardiac Conference Thursday through Saturday January 22 24 1976 at Vail Colorado This course will provide a review of some of the recent advances in recognition and management of a selected variety of cardiac problems and is approved for 1? hours continuing Medical Education credit Registration for the 3 days is $75 00 For additional information write Colorado Heart Association 4521 East Virginia Ave Denver Colo 80222 or call 303-399 2131

Postgraduate course on thrombosis

The American Heart Association Council on Thrombosis will conduct a postgraduate course entitled "Thrombosis Current Concepts of Diagnosis and Treatment" to be held February ? through 4 1976 at the Given Institute of Pathobiology Aspen Colorado Co-sponsors are the Colorado Heart Association and the University of Colorado Office of Continuing Education University of Colorado Medical School. Course directors will be Drs. E Genton and J Hirsh.

For further information contact Office of Continuing Education University of Colorado Medical School 4200 East 9th Ave Denver Colo 802?0

Postgraduate course in intensive care

The Department of Anesthesia in cooperation with Extended Programs in Medical Education University of

His Bundle Electrocardiography and Clinical Electrophysiology By Onkar S Narula Philadelphia 1975 F A Davis Company 472 pages Price $35 00

This book covers a highly specialized subject His bundle recording and function have engaged the interest of electrophysiologists and cardiac catheterization physicians in recent years Although the subject of His bundle recording has limited clinical applications at present because of the nature of the recording technique this book represents a good single source of material on the subject The contributions are numerous. The subjects discussed include anatomy electrophysiology techniques, normal and abnormal conduction A V nodal pathways, clinical disorders of A V node and bundle of His function and other aspects of His bundle recording Anyone who is studying the His bundle should study this book edited by Narula It presents extensively and very effectively the problems and clinical applications of His bundle function and recordings

Spatial Analysis of the Electrocardiogram A Program By Irwin Hoffman M D Julien H Isaacs, M D James V Dooley M D Phil R Manning and Donald A Dennis Ph.D St Louis 1975 The C V Mosby Company Price $6 95

This booklet is intended for the beginner interested in the principles of spatial vector analysis of the electrocardiogram It briefly and clearly presents with very nice illustrations the problem of spatial orientation of electric cardiac vectors as considered in cardiology today It is a source of good teaching material which should interest beginners in electrocardiography This is a paperback booklet effectively presented as a teaching manual

Books received

Anemia From Molecule to Medicine By Isaias Raw M D Boston 1975 Little Brown & Company 264 pp Price $10 95

Textbook of Medicine Edited by Paul B Beeson M D and Walsh McDermott M D Philadelphia 1975 W B Saunders Company 2200 pp Price $32 00

Clinical Recognition and Treatment of Diabetic Vascular Disease By John A Colwell M D Ph D Springfield Ill 1974 Charles C Thomas Publisher 73 pp Price $9 50

Laboratory Diagnostic Procedures in the Rheumatic Diseases 2nd ed Edited by Alan S Cohen M D Boston 1975 Little Brown & Company 409 pp

Dr Paul Dudley White What He Bequeathed to Science and Humanity By John P Arcieri M D New York 1974 Alcmaeon Editions 99 pp

The Story of Medicine By Petros De Baz M D New York 1975 Philosophical Library Inc 99 pp Price $6 00

Beta adrenergic Blocking Agents in the Management of Hypertension and Angina Pectoris Proceedings of an International Symposium held in Florence Italy April 6 1974 Edited by Bruno Magnani, M D New York 1975 Raven Press, Publishers 190 pages Price $10 00

Psychological Aspects of Myocardial Infarction and Coronary Care Edited by W Doyle Gentry and Redford B Williams Jr St Louis 1975 The C V Mosby Company 149 pages Price $6 95

Announcements

Symposium on cor pulmonale *chronicum*

The first common international congress of the European Society of Cardiology and the European Society of Physiology of Respiration will feature a symposium entitled "Cor pulmonale chronicum" to be held in Munich on March 4 through 6 1976. The program will cover the definition epidemiology pathology and pathophysiology of cor pulmonale chronicum. Clinical presentations will include clinical course diagnosis therapy prognosis and prevention.

For registration and other information contact PD Dr S Daum, I Medizinische Klinik and Poliklinik der Technischen Universitat, 8000 Munich 80 Ismaninger Str 22 Telephone (089) 4140-2353

Symposium on pediatric cardiology

The Johns Hopkins University is sponsoring the Helen B Taussig International Symposium on Pediatric Cardiology May 24 through 26 1976 at the Johns Hopkins Medical Institutions, Baltimore Maryland The Symposium is endorsed by the American Academy of Pediatrics and the Committee on Cardiovascular Disease in the Young of the American Heart Association Tuition is $150 00 and the program qualifies as an approved course in Continuing Medical Education enabling physicians who attend to qualify for 24 credit hours (in Category 1) towards the Physicians Recognition Award of the American Medical Association.

The ten major sessions will consider Tetralogy of Fallot Rheumatic Heart Disease Hypertension and Hyperlipidemia in the Young The Sick Infant Advances in Medical Management The Sick Infant Advances in Surgical Techniques The Sick Infant Problems After Surgery Society and the Child with Cardiovascular Disease Cardiomyopathies The International Scene Cardiomyopathies New Approaches to Diagnosis and Therapy and Etiology of Congenital Heart Disease

For further information contact Glenn C Rosenquist M.D Symposium Director CMSC 274 The Johns Hopkins Hospital, Baltimore Maryland, 21205 Call (301) 955 3611

Exercise testing in clinical practice

The University of Texas Health Science Center at Houston Division of Continuing Education, and Medical School announce a program *Exercise Testing in Clinical Practice* to be held March 5 1976 at The University of Texas Medical School Auditorium Houston Texas Co-sponsor—Baylor College of Medicine

The effects of exercise on the cardiovascular system are important in the diagnosis and the assessment of cardiovascular function in patients with heart disease In this course particular emphasis is placed on the diagnosis and management of coronary heart disease The significance of electrocardiographic changes including cardiac arrhythmias is discussed. Other topics are the effects of exercise on coronary risk factors and in the evaluation of patients following coronary bypass surgery The value of exercise in the post infarction patient and the effects of exercise on coronary blood flow are included. The cardiovascular response to the ordinary social smoking habit and the relation of orthostatic tolerance to cardiovascular stress are discussed

For further information contact The Office of the Director The University of Texas Health Science Center Division of Continuing Education, P O Box 20367 Houston Texas 77025 Call (713) 792-4671

Current problems in intensive care

The Department of Anesthesia in cooperation with Extended Programs in Medical Education University of California School of Medicine San Francisco California is sponsoring a postgraduate course "Current Problems in Intensive Care—Pulmonary Care" This course is designed to cover both theoretical and practical aspects of the causes, diagnosis and treatment of pulmonary edema. The course will be held in the Colonial Room of the St. Francis Hotel, Union Square San Francisco California, on April 1 and 2 1976 fee $100 00 The program is acceptable for 9 hours Category I credit toward the Certificate in Continuing Education for the California Medical Association and The American Medical Association.

For Registration information contact Extended Programs in Medical Education, Room C-135G University of California San Francisco CA 94143 Phone (415) 666-2483 or 666-2894 For program information call (415) 666-4251

Cardiac conference

The Colorado Heart Association presents the High Country Cardiac Conference Thursday through Saturday January 22 24 1976 at Vail, Colorado This course will provide a review of some of the recent advances in recognition and management of a selected variety of cardiac problems and is approved for 12 hours continuing Medical Education credit Registration for the 3 days is $75 00 For additional information write Colorado Heart Association 4521 East Virginia Ave., Denver Colo 80222, or call 303-399 2131

Postgraduate course on thrombosis

The American Heart Association Council on Thrombosis will conduct a postgraduate course entitled "Thrombosis, Current Concepts of Diagnosis and Treatment" to be held February 2 through 4 1976 at the Given Institute of Pathobiology Aspen, Colorado Co-sponsors are the Colorado Heart Association, and the University of Colorado Office of Continuing Education University of Colorado Medical School. Course directors will be Drs. E Genton and J Hirsh.

For further information contact Office of Continuing Education University of Colorado Medical School, 4200 East 9th Ave Denver Colo 80220

Postgraduate course in intensive care

The Department of Anesthesia in cooperation with Extended Programs in Medical Education, University of

California School of Medicine San Francisco is sponsoring a postgraduate course Current Problems in Intensive Care—Pulmonary Edema on April 1 2 1976 at the St Francis Hotel San Francisco which is acceptable for 9 hours Category I credit toward the Certificate in Continuing Education fee $100 00 Write or call Extended Programs in Medical Education Room 569 U University of California San Francisco CA 94143 *Telephone (415) 666-4251*

1976 1977 Johananoff International Fellowship for Advanced Biomedical Studies

Applications are invited for the 1976 1977 Johananoff International Fellowship for Advanced Biomedical Studies. It offers a distinguished scientist internationally recognized for outstanding contributions in cancer chemotherapy and/or immunology, cardiovascular pharmacology, neuropsychopharmacology or drug metabolism the opportunity of spending his or her sabbatical year at the Mario Negri Institute for Pharmacological Research in Milan Italy The *one-year $15 000 award includes stipend and travel*

The task of the Johananoff Fellow will be to prepare a comprehensive critical review on a well-defined subject within his competence containing suggestions for new research directions *This review will be presented in a special lecture* and will be published *in extenso* Eligible candidates must be non Italian citizens, affiliated with academic non profit or governmental institutions

Applications for 1976 1977 should be airmailed no later than January [illegible] 1976 and should include curriculum vitae list of publications and pertinent reprints, and a 250 word outline of the proposed study Applications or requests for further information should be sent to Johananoff Fellowship Committee Istituto di Ricerche Farmacologiche Mario Negri 62 Via Eritrea 20157 Milan Italy

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Editorial

The cardiologist's responsibility for preventing coronary heart disease

Richard Turner
Edinburgh Scotland
Keith Ball
London England

Coronary heart disease (CHD) is the commonest cause of premature death in the western world today and in many countries its incidence is increasing In America it is said that one man in five will develop symptoms before the age of 60 and one in three will have some form of symptomatic arterial disease Early death from acute myocardial infarction amounts to about 40 per cent Four times as many men as women die from CHD before the age of 65 resulting in a large number of widows and fatherless children caused each year by CHD alone Most deaths occur outside hosptial and too rapidly for medical care In many cases sudden death is the first and consequently the last manifestation

There is no prospect of spontaneous improvement in this situation

That environmental factors are largely responsible is indicated by the increasing incidence especially in younger men by the wide variation in prevalence of CHD between countries and between different regions of the same country by the development of CHD in migrants from poor to relatively affluent countries and by the wartime decline of CHD in food restricted Europe It follows that CHD should largely be preventable

At present there is too little relevant action Time effort and money are mainly spent on coronary care units coronary ambulances and even coronary arterial surgery and cardiac transplantation—although when symptoms first appear the underlying disease is likely to be far advanced

Secondary prevention although often neglected is second best

Only primary prevention could be really effective and since coronary arterial disease often starts in youth and is of slow development prevention should start early in life

Although there are gaps in our knowledge we believe that enough is already known not only for any doctor to apply a rational program of preventive treatment for his patients and their close relatives but to warrant examining apparently healthy persons to detect those at high risk[1]

Epidemiologists nutritionists and others principally interested in research can perhaps view the situation with relative equanimity hopefully awaiting positive results from more research and further trials but physicians with clinical responsibilities must give advice on the balance of

From the Department of Medicine University of Edinburgh, Edinburgh, Scotland, and the Central Middlesex Hospital, London England.

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Reprint requests to Dr Richard Turner Department of Medicine University of Edinburgh, 12 George Square Edinburgh EH8 9JZ United Kingdom.

current evidence Where probability of benefit is strong and the advice unharmful they are surely failing in their duty *not* to take appropriate action

Certain risk factors which have been identified are almost certainly causal and preventable We therefore recommend regular health examinations for their detection This is surely as reasonable as going to the dentist and much more important At present automobiles get better service

High risk groups

High risk groups include all patients with symptomatic disease and their near relatives all with hypertension or diabetes or with a strong family history of hypertension and/or atherosclerotic disease and all found on examination to have hyperlipidemia or a combination of several risk factors

We have found that about 20 per cent of middle aged men fall into these categories

Risk factors

Smoking About one half of the excess deaths in cigarette smokers are cardiovascular in origin and many of them are sudden[2] In the U K deaths from CHD in men aged 35 to 44 almost doubled between 1950 and 1967[3] which parallels the rapid increase in smoking between 1930 and 1945 Heavy smoking is especially frequent in relatively young men who die from myocardial infarction

The mortality rate from CHD 40 years ago was far higher in the professions than in unskilled laborers but since then the lowest paid have developed the highest mortality rate[4] This may in part reflect changing smoking habits Whereas cigarette smoking from 1955 has fallen considerably in the better educated it has risen in the others

Recent work has emphasized the importance of carbon monoxide (CO) in the development of CHD in smokers[5] Carboxyhemoglobin levels up to 15 per cent have been found CO not only induces hypoxia but also increases endothelial permeability and may thus enhance atherosclerosis We have found that many cigarette smokers who change to cigars continue to inhale and maintain raised COHb levels[6]

We have also found that smokers who change to very low tar and nicotine cigarettes may smoke more but their COHb levels are lower than when they smoked medium tar and nicotine cigarettes[7] Smokers with COHb levels over 5 per cent have been found to have more than 20 times the incidence of CHD than those with levels below 3 per cent[8]

Several studies have shown the benefit of stopping cigarette smoking A rapid fall in death rates from CHD occurs in the first year and after 10 years rates approach those of life long nonsmokers

In the combined results from Edinburgh and London we have found that about 60 per cent of 243 male survivors of acute myocardial infarction who had been smokers and advised to stop were still nonsmokers one or more years later[9]

Prevention must start before the age of 10 Children are unimpressed by the chances of cancer or a coronary by the age of 50, but are influenced by example and by the antisocial aspects of smoking Herein lies the opportunity Doctors should understand the scientific basis for linking smoking and CHD and this we have recently reviewed[10]

Hypertension There is epidemiological, clinical pathological, and experimental evidence that hypertension accelerates the development of[11 12] atherosclerosis and that this is increased if hyperlipidemia is present There is a nearly linear relationship between the height of the blood pressure and the risk of CHD It is a powerful predictor

The lipid concentration of the arterial wall is related to that in the blood the filtration pressure (blood pressure), and the permeability of the wall which may be increased by the hypoxia which results from smoking

Experimentally it has been shown that lowering raised blood pressure retards the development of atherosclerosis[11]

Although it has not yet been demonstrated that the treatment of hypertension will reduce the incidence of CHD, the attempt has not been made in its early stages It is reasonable to expect that benefit would result if treatment were begun much earlier than is usually the case However, since the incidence of hypertensive heart disease and stroke can be greatly reduced by treatment the detection of hypertension is in any case important

The bulk of the hypertensive problem lies with the many individuals who are unknown to their practitioners and can be detected only by health examinations There is no escape from this

dilemma We believe that there are needless fears that anxiety and introspection would often be induced or that the numbers found to have hypertension would be too great for management Following an initial medical assessment by the physician much of the management could be supervised by community nurses working with family doctors

Treatment of other coronary risk factors together with the elimination of added salt from the table and in cooking may alone suffice to control the blood pressure in those with borderline or mild hypertension Others including most with severe and moderately severe hypertension require drug therapy which will largely protect them from hemorrhagic strokes left ventricular failure and acceleration of renal failure However since they still tend to die prematurely from CHD attention to all risk factors is very important This especially applies to hyperlipidemia and smoking

The control of blood pressure without significant side effects is usually possible if an appropriate combination of drugs is used and those with a relatively high incidence of side effects such as guanethidine methyl dopa rauwolfia and clonidine are avoided Oral diuretics are essential only for the control of fluid retention They are often used in hypertension but the long term effects of induced hypokalemia are unknown and some develop hyperglycemia or hyperuricemia

We think a beta blocker should nearly always be given either alone or in combination since the blood pressure is thereby reduced in both lying and standing postures Side effects are uncommon and rarely severe postural hypotension does not occur and there are many potential advantages in reducing catecholamine secretion

Most patients with more severe hypertension will in addition require another drug For the last 10 years we have found that debrisoquine has many advantages and is the best of the adrenergic blockers It is remarkably free from side effects and provided that the initial dose is small and only slowly increased postural symptoms can usually be avoided

New methods of drug therapy are under study but not established

Hyperlipidemia atherosclerosis and diet

Population studies have shown that there are close links between hyperlipidemia atherosclerosis CHD and diet[5] Their interrelationships are complex and since there is considerable variation between individuals other factors must be involved The evidence suggests however that there are basically nutritional disorders

Secondary thrombus formation and its complications vary considerably despite similar severity of atherosclerosis so that the latter is more an index of susceptibility to CHD than to its incidence and the factors responsible are not identical[15]

There is also a vast amount of epidemiological clinical pathological and experimental work to indicate that hyperlipidemia influenced by inherited predisposition and habitual diet not only has a high association and hence is a strong predictor but is a causal factor in the etiology of atherosclerosis and CHD

Nevertheless there are gaps in knowledge and the crucial evidence that the incidence extent and mortality rate of CHD can with certainty be reduced by dietary means alone is not at present available The trials which have been reported are promising but have had imperfections of design and so are not accepted as conclusive Ideally they should begin in childhood before atherosclerosis is advanced as it often is in middle age but this would add to the difficulties referred to below

In the absence of proof and in such a serious situation decisions must be made and advice given or withheld on the basis of probability Paradoxically far stronger evidence is often demanded for preventive measures that is ever considered necessary for giving drugs or advising surgical treatment

The evidence supporting a causal relationship between hyperlipidemia and CHD and hence justifying dietary advice includes the following facts

- CHD is rare in populations with low mean plasma cholesterol levels
- CHD at a relatively young age is common in patients with familial hyperlipidemia
- There is an almost linear relationship between plasma cholesterol levels above 200 mg per 100 ml and the incidence of CHD[4]
- Recent studies suggest that hypertriglyceridemia is probably an independent risk factor
- Plasma lipids are mainly derived from the food and can be raised or lowered by changing eating habits

- The hallmark of the atheromatous plaque is the accumulation of cholesterol in it
- The concentration of cholesterol in the arterial wall is in proportion to that in the plasma [17]
- It has been repeatedly shown that atherosclerosis can be produced in many species by feeding a high fat-high cholesterol diet but, most impressively, in primates nearest to man atherosclerosis and its complications of myocardial infarction and peripheral gangrene has been induced by feeding a Western type diet [18]
- Furthermore the pathological changes in the arterial wall regress on changing back to a natural diet [19]
- The clinical counterpart in man is regression in cutaneous manifestations of hypercholesterolemia after treatment by diet or drugs
- Finally as mentioned above, recent dietary trials in man are encouraging [9,22]

Variation in plasma lipids Although it is clear that atherosclerosis and plasma lipids are mainly nutritionally determined lipid levels vary in populations and in individuals living on a similar diet and even between those kept on an identical diet in a metabolic unit Consequently there must be variable inherent susceptibility to develop atherosclerosis Nevertheless in all people lipid levels are much influenced by diet

Not only is there considerable variation between individuals, but in the same individual from time to time and even from day to day The reasons for this are not fully understood but include dietary and nondietary factors Dietary factors include total calories total fat saturated and unsaturated fat, refined and unrefined carbohydrate, cholesterol sugar, and alcohol Nondietary factors include smoking exercise, stress, season, posture changes in weight recent myocardial infarction and drugs

It is clearly important that measurement of cholesterol and triglycerides should be accurate but this is far from being the case in many laboratories Quality control studies have shown remarkable variation in the reported results from different laboratories on the same specimen of blood

These are unfortunate facts but they must be kept in mind Nevertheless, in the vast majority of patients and in population studies only a single measurement is made and more than this may not be practicable

Plasma lipoproteins and lipids The classification of plasma lipoproteins introduced by Fredrickson Levy, and Lees[23] and the modifications suggested by others were based on studies of familial hyperlipoproteinemias They are important for the understanding of metabolic abnormalities and for research but, unfortunately, have been inappropriately applied to the general population

Measurement of lipoproteins are unnecessary for the management of the great majority of coronary patients and those at high risk from developing the disease They are needed only for the few with true familial hyperlipoproteinemia—that is with a clear family history, and where eating habits have not been the main factor and for the few who fail to respond to simple treatment The facts that inherited predisposition and habitual diet are important for all with hyperlipidemia does not mean that they can be classified into Fredrickson s types of familial hyperlipoproteinemia At present there is no evidence that measurement of lipoproteins is a better guide to prognosis or treatment than that of plasma lipids

Diet Reduction in lipid levels is likely to have a favorable effect in all at high risk but most of them are unknown to their practitioners Consequently it is reasonable to advise some modifications in diet for the population as a whole many of whom have relatively high lipid levels by ideal standards that is to say above those in countries with little or no atherosclerosis If regular health examinations were accepted and lipid levels known advice could be given on an individual basis but at best it will take some years before such routine screening can be introduced

The principles of diet are not difficult to learn nor does adherence to them entail much hardship Habits can often be changed if the reasons are appreciated There need be no absolute taboos and general rules can be forgotten when dining out or on other special occasions

In the obese calorie restriction should include reduction in total fat and carbohydrate intake Saturated fat sugar and salt should be reduced with a switch from saturated to polyunsaturated fat at table and in cooking

The same basic diet for lowering plasma lipids can be advised for all coronary patients and those

at high risk, with modifications for particular circumstances.

Obesity, hypercholesterolemia, and hypertriglyceridemia are undesirable. The aim should be to eliminate adiposity and maintain cholesterol and triglyceride levels in the lower physiological range.

If cholesterol levels are inadequately reduced, there must be greater emphasis on avoidance of saturated fat and eggs, and if triglyceride levels are inadequately reduced, on avoidance of sugar and alcohol. The benefits of increasing energy expenditure by regular exercise should also be explained.

Should this regime be inadequate, the next step is to give clofibrate, which is tolerated by almost all without side effects of any kind.

Only a few require more detailed laboratory investigation of lipoproteins and individual drug therapy.

Obesity

All insurance statistics have shown that obesity is adverse to health, mainly from cardiovascular and cerebrovascular diseases, and that life expectancy improves with its reduction. It is probably not so much obesity itself, however, which is a high risk factor as the often associated hypertension, hyperlipidemia, and impaired glucose tolerance, all of which improve with its reduction. In addition, obesity discourages the taking of exercise.

In treatment it is important that emphasis should be laid on regular exercises as well as diet because of its intrinsic benefits. One hundred calories less consumed and 100 more expended each day would lead, over the course of a year in an obese person, to the loss of about 20 pounds in weight.

Exercise

There is much to indicate that physical inactivity is one important factor in the high prevalence and increasing incidence of CHD. Man did not evolve as a sedentary being, and lack of regular exercise is of recent development. The physiological responses to regular exercise, the value of training in rehabilitation after myocardial infarction, and in improving exercise capacity in patients with angina of effort all support its role in the primary prevention of CHD.

Between the pioneer studies of Morris and associates[3] more than 20 years ago and their most recent paper, there have been many reports on the value of exercise. Conclusions based on retrospective analyses can be criticized owing to inherent defects which cannot be avoided. Almost all observational studies,[4] which include leisure activities, have shown a beneficial effect from exercise in reducing the incidence, severity, and morbidity of CHD. Further work of a similar kind is unlikely to bring stronger evidence. Only controlled prospective intervention studies could produce a conclusive answer, but there would be great difficulties in carrying them out and, as in the case of dietary trials, expense alone would probably be prohibitive.

Regular exercise, if sufficiently vigorous, greatly improves cardiopulmonary function and exercise tolerance in healthy individuals.[7] Maximum oxygen uptake and its transport, together with oxygen extraction by the tissues, are increased, myocardial oxygen economy is improved with less oxygen required for a given amount of work, and myocardial vascularization is almost certainly increased.[8] Peripheral mechanisms also play a part in improving regional blood flow.

Most coronary risk factors are favorably modified by exercise. Hyperlipidemia, postprandial lipemia, and hyperglycemia are all reduced. On the same calorie intake there is weight loss in the obese. Peripheral vascular resistance is lowered so that blood pressure is reduced. Fibrinolytic activity is increased and platelet aggregation reduced so that thrombus formation is likely to be impeded.

All forms of rhythmical dynamic exercise are beneficial if sufficiently vigorous to cause sustained tachycardia. Walking, running, jogging, and climbing stairs or hills can be carried out throughout the year without expense or special facilities. Swimming and cycling are excellent for improving exercise tolerance. Half an hour's brisk walk each day, together with more vigorous exertion for half an hour three times a week, can greatly improve cardiopulmonary fitness. The major problem is that of motivation.

Although older subjects and those at high risk may need a medical examination before undertaking an exercise program, most healthy people do not, provided they start gently and gradually increase the vigor of activity.

All forms of exercise are useful for energy expenditure.

Exercises (calisthenics) are useful for warming up and for improving muscle tone and joint mobility to avoid soft tissue injuries but only sustained tachycardia for ten minutes or more will improve exercise tolerance and cardiopulmonary fitness to a degree which is likely to be protective to the myocardium All these aspects have been reviewed [27]

Exercise has to be built into our way of life, seeking every opportunity throughout each day

Stress

Many workers have shown associations between CHD and emotional stress Angina myocardial infarction pulmonary edema, and sudden death can be precipitated by arguments driving an automobile excitement or bereavement These effects are thought to be due to catecholamine secretion

The ambitious aggressive competitive way of living may over the years, lead to CHD although stress can also lead to other risk factors such as smoking and overeating We have found that our coronary patients cannot be conveniently classified into personality types because patients and controls each include a variety of characteristics in varying proportion It is the reaction to stress which is important

It has often been noted that preceding a myocardial infarction there have been weeks or months of unusual stress A direct relationship between stress, atherosclerosis and thrombus formation is more difficult to prove but is supported by the known mechanisms of catecholamine secretion which include increase in blood pressure, heart rate circulating lipids, and platelet aggregation

Advice relating to the reduction of sympathetic overactivity should be undertaken by personal counselling on avoiding unduly stressful situations including conflicts and confrontations at home and at work, on stopping smoking and on the importance of regular exercise which improves autonomic balance Beta blocking drugs are useful while personal readjustments are being made

Other risk factors

Most other risk factors which have been considered do not at present have practical implications other than the measures discussed above They include diabetes and subclinical carbohydrate intolerance, hyperuricemia and various trace elements Diabetes in particular requires a very vigorous approach against the recognized risk factors

Additive factors

Risk factors are not only individually adverse but often interrelated, cumulative, and possibly synergistic This has been shown for various combinations of hypertension, hyperlipidemia, smoking, obesity, and physical inactivity A strong family history of relevant disorders is also important because it reflects inherited predisposition

These facts should be kept in mind, particularly when making decisions on whether to treat borderline conditions such as hypertension In a multifactorial disease control of a single factor is unlikely to have a major impact and it is clearly important to aim at controlling them all

Vigorous approach to secondary prevention

The physician should regard each new patient with symptomatic CHD as one in whom primary prevention has failed usually through not having been tried Such a person should be accepted as an opportunity and a challenge for a vigorous and even aggressive approach to secondary prevention In addition each patient provides access to the family who are also likely to be at high risk in order to screen for coronary risk factors and give appropriate advice on primary prevention The aim should be to eliminate or greatly reduce each coronary risk factor

Myocardial infarction Vigorous secondary prevention after myocardial infarction should be a major responsibility for every cardiologist Such an approach is warranted because the prognosis is relatively poor in survivors of reinfarction Conventional advice often amounts to little more than Cut down on smoking lose some weight, and otherwise take it easy Rather we should aim to eliminate smoking hyperlipidemia, hypertension and obesity encourage a program of regular exercise and pay individual attention to avoidable stress Most patients should feel much fitter 6 months after their attack than they did before

We have found that acceptance of advice given in hospital is assisted by an explanatory booklet by regular follow up interviews and by visits from a community nurse acting as a link between hospital and home Not only can she ensure that the patient understands what should be done but

she can give further advice on details advising the wife on the optimum diet for her husband and children and emphasizing the importance of a smoke free home and of regular exercise

Angina of effort Most patients with angina of effort can be much improved by proper medical management which is too often neglected Surgical treatment is needed only in the small number who fail to respond Unless it can be shown in properly controlled trials that the expectation of life is thereby improved these hazardous investigations and palliative operations should not take precedence over well tried medical management The risks and complications of surgical treatment would certainly not be acceptable to the FDA if a drug rather than an operation were under consideration

The cornerstone of management is a definitive exercise program gently begun and gradually increased short of pain dyspnea or fatigue This is facilitated by the invariable use of prophylactic trinitrate and the routine use of a beta blocking drug such as propranolol or oxprenolol up to at least 800 mg daily if necessary At the same time there should be a vigorous attack on *all* associated coronary risk factors

We have found that this approach is successful in the great majority of patients

Although these aspects of secondary prevention in treatment are important the real answer to the coronary problem lies in primary prevention

Primary prevention

Health examinations The concept that prevention is better than palliation or cure is universally held but often little more than lip service is paid to this obviously sensible principle

The detection of those at high risk with the object of giving preventive advice can be done only by screening but this term has led to misunderstanding Mass population screening is a formidable concept suggesting publicity and considerable expenditure on facilities and personnel with the problem of dealing with the large numbers detected Rather do we recommend regular health examinations carried out by personal physicians as part of normal health care needing few extra facilities although assistance would be required from health workers

We have found that community nurses are interested keen and capable of helping with the initial health examination and in the giving of advice and sometimes treatment such as for hypertension In addition by visiting the home they can advise on food smoking exercise and stress

Nurses can also form an invaluable link between hospital and home in rehabilitation and secondary prevention after acute myocardial infarction and in extending advice to primary prevention in the family

Some contend that health examinations are not indicated at the present time because (1) The evidence that risk factors are causal is only circumstantial (2) Prediction is not yet sufficiently accurate (3) There is no proof that intervention would reduce the incidence of CHD (4) Unwarranted anxiety might be induced (5) Facilities will not always be available for dealing with conditions found (6) Some conditions would be disclosed for which as yet no adequate treatment exists Consequently it is considered that action should await more research and further trials

Our viewpoint is that although more research is certainly needed especially as regards better predictors of CHD and underlying mechanisms which might be influenced by treatment enough is already known to justify preventive action

In the United States much is being done by the example and enthusiasm of individual physicians and research teams In the United Kingdom a little is being done by a few However the problem is a public health problem of national dimensions There are immense implications for reorientation including acceptance of the principle of regular health examinations followed by the giving of informed advice

Periodic health examinations are made more often in the U S than in the U K After this has been done however advice on primary prevention should be given by physicians who are aware of the facts and have learned how best to put the message across Most doctors are not motivated toward preventive medicine are unfamiliar with the evidence justifying action and may consider that they cannot afford the necessary time In the U K the basis of health care is *general practice* and almost all are registered with a *family doctor* routine health examinations could be introduced without need for special facilities, *undue extra* time or the fear that anxiety and introspection would be engendered An initial health examination when registering with a family doctor would soon be accepted as normal practice

The essential prerequisites are motivation an

up to date age sex register one or more community nurses and secretarial help

In the U K more than 60 per cent of patients consult their doctor each year and the average turnover of new patients and those dying or leaving the district is about 10 to 15 per cent per annum Within five years few would not have consulted their doctor and these could be visited by the community nurse

No proof No proof—the evidence is only circumstantial is the cry too often heard with regard to prevention A growing number of physicians believe however that the risk factors discussed are almost certainly causal and that benefit would result from their reduction As in many areas of medical practice, strong probability rather than proof must govern action The effectiveness of many treatments lacks proof yet they are widely prescribed

Large scale prospective intervention studies which alone could bring proof are unlikely to reach conclusions at any rate for many years Owing to great difficulties and cost, single factor trials of adequate size may never be carried out The case of dietary trials may be taken as an example Recently it was estimated that a satisfactory full scale trial would require between 24 000 and 115 000 participants would need to last for 7 to 10 years and would cost between $500 million and $1 000 million [29] It was considered that there would be great problems because of dropouts the fact that about 20 per cent of Americans change their place of living each year that participants would probably be motivated to change other risk factors and controls to modify their habits owing to a change in the climate of opinion and thus influence the study Also the trial might never be finished and if it were the results might be inconclusive

For similar reasons conclusive evidence on the value of regular exercise might be even harder to obtain and a trial in relation to stress would be impossible

There is no need for stronger evidence that smoking hypertension and obesity are adverse to health

Prevention in childhood

Since atherosclerosis frequently starts in youth preventive measures should begin early Children could be brought up virtually free from coronary risk factors The first step lies in infant feeding There are many advantages in breast milk but in the coronary context most important are the avoidance of obesity (which is easier than when substitutes and supplementary foods are given) of hyperlipidemia and of a taste for sugar and salt

Obesity in infancy frequently precedes that in childhood and adult life yet still it is the traditional bonny baby who gets the prize rather than the parents who should be allotted the booby prize

Babies vary in their requirements as do adults and excessive weight gain should be immediately countered

Breast milk has been gradually evolved toward perfection over millions of years and for a normal baby born to a healthy mother is an all sufficient food for the first few months

Cow s milk is unnatural, except for calves The fat is more saturated than in human milk and less well absorbed The sodium content is much higher and this could be a factor in later hypertension Recently it has been suggested that cow s milk protein has antigenic properties which for some may be a causal factor in atherosclerosis [10]

Appropriate weaning should include limitation of saturated fats and their partial replacement with polyunsaturated fat with a high linoleic acid content together with avoidance of added sugar and salt A taste for healthy foods should be inculcated early, since good feeding habits are likely to persist

School meals require review with the same principles in mind All this implies a changed attitude by nutritionists and all concerned with health education

Summary

The recent increase in coronary heart disease is real and the causes must mainly be environmental Consequently the condition should largely be preventable The application of what is already known is likely to be a far more effective way of reducing the mortality rate than all attempts at palliative treatment but vigorous action will be necessary Much greater sums are being expended on coronary care units and cardiac surgery than in preventing the need for them although there is little evidence that they have significantly lowered the over all mortality rate

Conventional treatment is immensely expen

sive Prevention could in the long run be much cheaper

Cardiologists on their own are unlikely to succeed in a program of prevention They need the help of many others including community nurses nutritionists public health workers sociologists and of course general practitioners but they have responsibility for leadership and for providing background knowledge

For the detection of certain risk factors health examinations are necessary and should be part of general practice Also advice is best given on an individual basis The chief known risk factors (hyperlipidemia hypertension smoking physical inactivity) could be controlled

CHD occurs in adults but atherosclerosis starts many years before Prevention should begin with appropriate infant feeding whenever possible with breast milk and continue into childhood when habits are formed and attitudes to life can best be influenced

It should be possible to bring up children virtually free from risk factors

It may never be possible to prove the effectiveness of such a multifactorial program by prospective controlled intervention studies but the evidence indicates strong probability The stakes are too high to delay action any longer Physicians daily give advice in areas where the evidence is much less certain

Such a program for the control of coronary artery disease is urgently needed and could become one of the most rewarding activities for the medical profession

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Prinzmetal's variant form of angina as a manifestation of alpha-adrenergic receptor-mediated coronary artery spasm Documentation by coronary arteriography

Hirofumi Yasue M D
Masato Touyama M D
Hirofumi Kato M D
Satoru Tanaka, M D
Fumiya Akiyama M D
Shizuoka City Japan

Prinzmetal's variant form of angina is characterized by recurring attacks of chest pain which, in contrast to classical angina occur at rest and are not precipitated by exercise or emotional stress and are associated with transient ST segment elevation in the electrocardiogram (ECG)[1,2] Prinzmetal and his co workers postulated that coronary arterial spasm was probably the cause of this syndrome and several recent reports[3-6] demonstrated arteriographically that severe coronary arterial spasm was indeed associated with the attacks We have reported that the attacks can be induced by the stimulation of alpha adrenergic receptors and speculated that spasm of a large coronary artery mediated by alpha adrenergic receptors was probably responsible for them[7]

The present study was designed to determine whether the alpha receptor-stimulation induced attacks are actually associated with the spasm of a large coronary artery

Material and methods

Four patients with Prinzmetal's variant form of angina were studied (Table I) The attack was recurring at 1 00 to 3 00 A M every night in Patient 1 at 1 00 to 5 00 A M every 2 or 3 nights in Patient 2, at 1 00 to 2 00 A M once or twice a week in Patient 3 and 2 00 to 5 00 A M every night in Patient 4, it was relieved by nitroglycerin in all four cases After the administration of propranolol, 40 mg orally at bedtime (9 00 P M) for 3 to 5 days the attacks became more severe and frequent occurring two or three times at 1 00 to 5 00 A M every night in Patient 1 once or twice at 0 00 to 5 00 A M every night in Patient 2 at 1 00 to 3 00 A M every 3 or 4 nights in Patient 3 and 3 to 5 times at 1 00 to 7 00 A M every night in Patient 4 The administration of propranolol was then stopped The attacks however did not occur during isoproterenol infusion (20 μg per minute) or Master's triple two step test In an attempt to induce the attack by stimulating alpha adrenergic receptors subcutaneous injections of epinephrine (0 4 to 0 5 mg) 3 hours after the oral administration of propranolol (40 mg) were given at 7 30 to 9 00 A M, with constant monitoring of blood pressure and ECG to all four patients Blood pressures rose heart rates decreased markedly and the attacks occurred 4 minutes 3 minutes 6 minutes and 4 minutes respectively, in Patients 1 2 3 and 4 after the combined administration of epinephrine and propranolol (Figs 1 2 and 3) The induced attacks were similar in all features to the spontaneous ones except for the epinephrine caused blood pressure elevation which persisted even after the subsidence of the attack by nitroglycerin and marked bradycardia After it was confirmed that these attacks could be induced by this combined administration of epinephrine and propranolol

From the Division of Internal Medicine and Thoracic Surgery Shizuoka City Hospital Shizuoka City Japan

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Reprint requests Hirofumi Yasue M D Division of Internal Medicine Shizuoka City Hospital Ote Cho Shizuoka City Japan 420

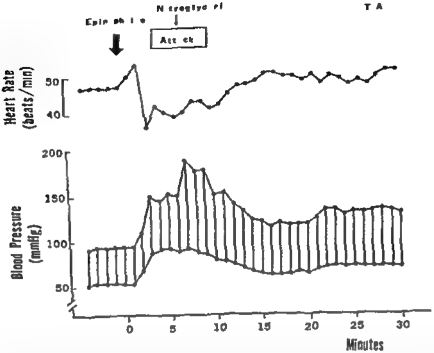

Fig 1 Case 1 The effects of the subcutaneous administration of epinephrine (0.5 mg) 3 hours after the oral administration of propranolol (40 mg) on blood pressure heart rate and anginal attack Epinephrine was given at the big arrow and nitroglycerin (0 3 mg) sublingually) at the small arrow

Table I ECG and coronary arteriographic findings in four patients with Prinzmetal's variant form of angina

Case No	Age	Sex	ECG at rest	ECG during the attack	Coronary arteriogram
1	6	M	Normal	ST elevation in Leads II III and aV	[illegible]0 per cent localized stenosis in the proximal portion of the right coronary artery left coronary artery normal
2	48	M	Normal	ST elevation in Leads II III and aV	Normal
3	53	M	Normal	ST elevation in Leads II III and aV	95 per cent localized stenosis in the midportion of the right coronary artery left coronary artery normal
4	6[illegible]	M	T inversion in Leads II III and aV	ST elevation in Leads II III and aV	90 per cent localized stenosis in the proximal portion of the right coronary artery 50 per cent localized stenosis in the proximal portion of the left circumflex artery left anterior descending artery normal

the attacks were again precipitated by this method on separate days this time selective coronary cinearteriography was done before during and after the attack with constant monitoring of ECG and blood pressure in all four patients Informed consent was obtained from each patient

Results

In Patient 1 the attack occurred 4 minutes after the injection of epinephrine (0 5 mg) The coronary arteriogram during the attack showed severe spasm of the right coronary artery at the proximal portion (Fig 4 *A*) and it took more than 2 0 seconds after injection of the contrast material before the distal parts could be visualized Normally it takes only 0 3 to 0 5 second after injection of the contrast material before the distal parts can visualized (personal observation) The attack disappeared about 2 minutes after nitroglycerin administration (0 6 mg sublingually) and the coronary arteriogram at this time showed

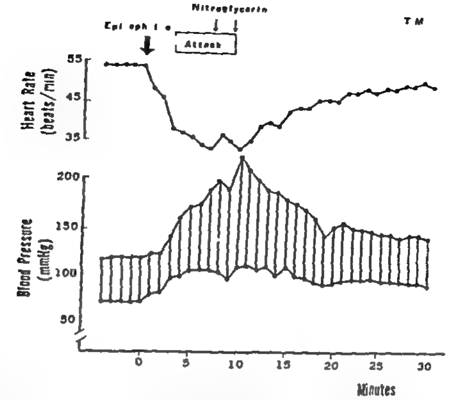

Fig 2 Case 2 The effects of the subcutaneous administration of epinephrine (0.5 mg) 3 hours after the oral administration of propranolol (40 mg) on blood pressure heart rate and anginal attack Epinephrine was given at the big arrow and nitroglycerin (0 3 mg two times sublingually) at the small arrows

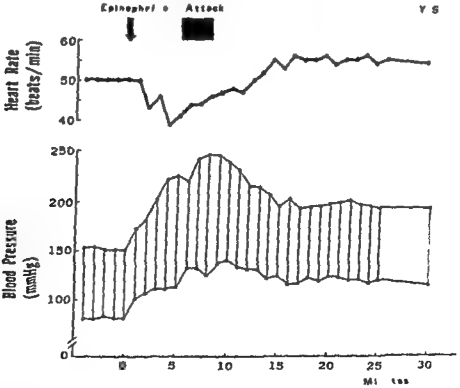

Fig 3 Case 3 The effects of the subcutaneous administration of epinephrine (0 4 mg) 3 hours after the oral administration of propranolol (40 mg) on blood pressure heart rate and anginal attack Epinephrine was given at the big arrow

a widely patent right coronary artery with about 50 per cent localized stenosis at the proximal portion (Fig 4 *B*) The ECG during the attack showed ST segment elevation in Lead III which returned to the baseline with the disappearance of the attack (Fig 5) The attack was again induced by the same method a week later and severe spasm of the right coronary artery was again demonstrated during the attack In Patient 2 the attack appeared 2 minutes after the injec

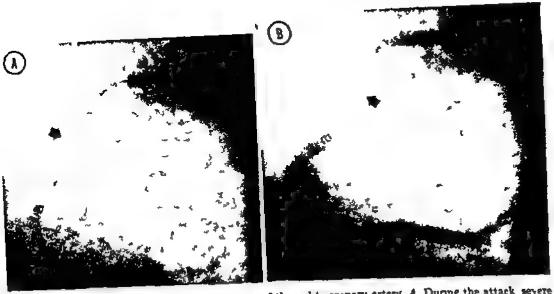

Fig 4 Case 1 Left anterior oblique cineangiograms of the right coronary artery *A* During the attack severe spasm of the right coronary artery occurred at the proximal portion (arrow) with extremely poor peripheral runoff *B* After the attack subsided with the sublingual administration of nitroglycerin (0 6 mg) the angiogram showed the widely dilated right coronary artery with an about 50 per cent localized stenosis at the site of the spasm (arrow)

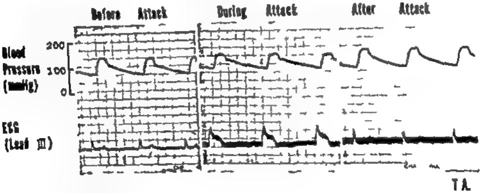

Fig [illegible] Case 1 The ECG during the attack (middle) showed ST segment elevation in Lead III which disappeared with the subsidence of the attack (right)

tion of epinephrine (0 5 mg) and the coronary arteriogram which had been normal before the attack (Fig [illegible] *A*) showed severe spasm of the right coronary artery at the proximal portion (Fig 6 *B*) and visualization of the distal parts after injection of the contrast material was markedly delayed to about 2 0 seconds during the attack The attack disappeared about 2 minutes after the sublingual administration of nitro glycerin The ECG during the attack showed ST segment elevation in Lead III which returned to normal with the disappearance of the attack (Fig 7) In Patient 3 the injection of epinephrine (0 4 mg) induced the attack 6 minutes later and severe spasm of the right coronary artery occurred at its midportion (Fig [illegible] *A*) the distal parts could not be visualized until about 1 5 seconds after injection of the contrast material during the attack The attack subsided about 1 minute after the administration of nitroglycerin (0 6 mg sublingually) and the coronary arterio gram at this time demonstrated the disappear ance of the spasm and the existence of a severe localized stenosis at the site of the spasm (Fig [illegible] *B*) The ECG during the attack showed T eleva tion in Lead III which disappeared with the sub sidence of the attack (Fig 9) In Patient 4 the attack occurred [illegible] hours after the administration of propranolol but before the injection of epinephrine the coronary arteriogram during the

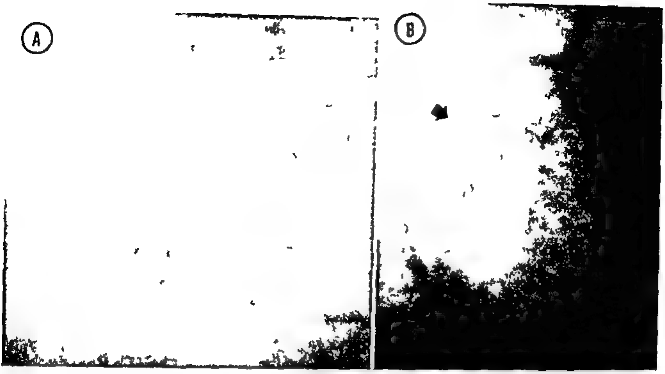

Fig ■ Case 2 Left anterior oblique cineangiograms of the right coronary artery A Before the attack the right coronary artery appeared normal with good peripheral runoff B During the attack severe spasm of the right coronary artery occurred at the proximal portion (arrow) with extremely poor peripheral runoff

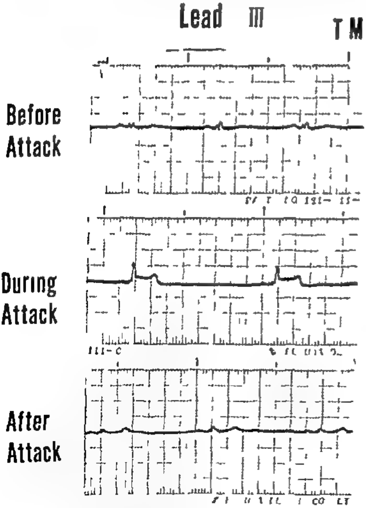

Fig 7 Case ■ The ECG during the attack (middle) showed ST segment elevation in Lead III which returned to the baseline with the subsidence of the attack (bottom)

attack showed severe spasm of the right coronary artery at the proximal portion and distal parts of it could not be visualized during the entire period of contrast material injection (Fig 10, *A*) The attack subsided about 3 minutes after the sublingual administration of nitroglycerin (0 6 mg) and the coronary arteriogram at this time (Fig 10 *B*) showed a widely dilated right coronary artery with a severe localized stenosis in the proximal portion The ECG during the attack showed ST segment elevation in Lead III which disappeared with the subsidence of the attack (Fig 11) Blood pressure which had been 120/82 before the attack rose to 148/102 during the attack and then returned to 118/86 after nitroglycerin and the attack

Discussion

We have reported that an attack of Prinzmetal s variant form of angina could be induced by the administration of epinephrine but not by that of isoproterenol and that the administration of phenoxybenzamine an alpha adrenergic blocker suppressed the attack but that of propranolol a beta adrenergic blocker, did not and have postulated that severe spasm of a large coronary artery mediated by alpha adrenergic receptors was probably the cause of the attack [1]

In the present study alpha adrenergic receptors were stimulated by the subcutaneous injec

Fig 8 Case 3 Left anterior oblique angiograms of the right coronary artery A During the attack severe spasm of the right coronary artery occurred in the midportion (arrow) with extremely poor peripheral runoff B After the attack subsided with the sublingual administration of nitroglycerin (0 6 mg) and angiogram showed a severe localized stenosis at the midportion but no spasm (arrow) of the artery

tion of epinephrine beta adrenergic receptors having been blocked by the prior administration of propranolol and the attack was induced repeatedly in all four patients confirming our previous report Severe spasm of the right coronary artery at the proximal portions actually occurred during the attack in association with ST segment elevation in the ECG and disappeared with the subsidence of the attack in all the four cases

These results strongly suggest that Prinzmetal s variant form of angina is caused by severe spasm of a large coronary artery mediated by alpha adrenergic receptors in the large coronary artery

Several recent reports also showed that attacks of Prinzmetal s variant form of angina are associated with severe spasm of a large coronary artery

Coronary arteries are supplied with both alpha (vasoconstrictor) and beta (vasodilator) adrenergic receptors and alpha receptors are predominant in the large coronary arteries[8 9] But coronary arterial tone is regulated primarily by the metabolic requirements of the myocardium increase in myocardial oxygen consumption causing coronary vasodilatation and neurogenic control of the coronary circulation is of lesser importance In the present study it is considered that myocardial oxygen consumption having

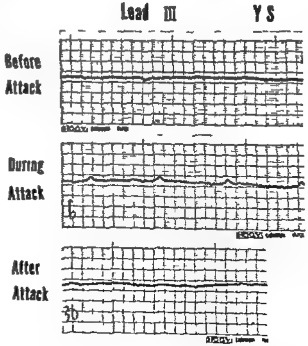

Fig 9 Case 3 The ECG during the attack (middle) showed T elevation in Lead III which disappeared with the subsidence of the attack (bottom)

been reduced by the prior administration of propranolol[11] the injection of epinephrine which is the most potent alpha adrenergic stimulator[8 9] with its beta adrenergic activity blocked by

Fig 10 Case 4 Left anterior oblique cineangiograms of the right coronary artery A During the attack severe spasm of the right coronary artery occurred at the proximal portion (arrow) its distal parts being not visualized during the entire period of the injection of the contrast material B After the attack subsided with the sublingual administration of nitroglycerin (0 6 mg) the angiogram showed the widely dilated right coronary artery with a severe localized stenosis at the proximal portion (arrow)

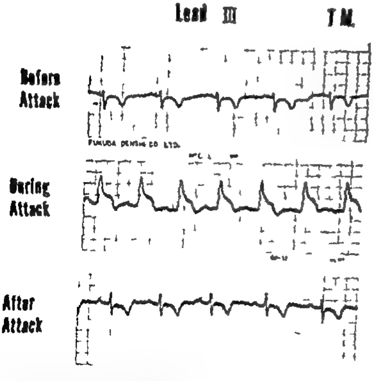

Fig 11 Case 4 The ECG during the attack (middle) showed ST segment elevation in Lead III which disappeared with the subsidence of the attack (bottom)

propranolol caused severe spasm of a large coronary artery by way of activating alpha adrenergic receptors in the large coronary artery

Many features of this syndrome could be easily explained on the basis of severe spasm of a large coronary artery as its cause The attack occurs at rest because myocardial oxygen consumption is reduced and coronary vasoconstriction develops during rest In addition the increased activity of the vagus nerve which occurs during rest[18] is believed to stimulate the sympathetic nerve to release norepinephrine[9] which in turn activates alpha adrenergic receptors in the large coronary artery The attack does not occur during exercise because myocardial oxygen consumption is increased and coronary vasodilatation develops An ST segment elevation in the ECG occurs during the attack because severe spasm develops at a large coronary artery and it is documented that temporary occlusion of a large coronary artery causes ST segment elevation without infarction[1]

Summary

In four patients with Prinzmetal's variant form of angina the attack was induced by the combined administration of epinephrine (0 4 to 0 5 mg given subcutaneously at 7 30 to 8 00 A M) and propranolol (40 mg given orally at 5 00 A M) Selective coronary cinearteriography was done before during and after the attack with constant monitoring of the ECG and blood pressure

Severe spasm of the right coronary artery

occurred at the proximal portion in association with ST segment elevation in Lead III during the attack and disappeared with the subsidence of the attack in all of them These results strongly suggest that severe spasm of a large coronary artery mediated by alpha adrenergic receptors is responsible for the attack of Prinzmetal's variant form of angina

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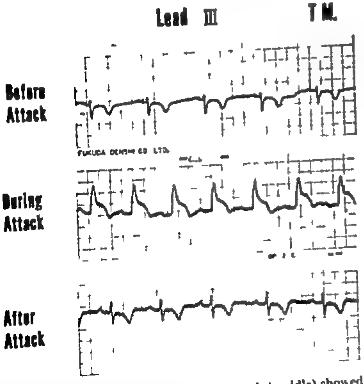

Fig 11 Case 4 The ECG during the attack (middle) showed ST segment elevation in Lead III which disappeared with the subsidence of the attack (bottom)

propranolol caused severe spasm of a large coronary artery by way of activating alpha adrenergic receptors in the large coronary artery

Many features of this syndrome could be easily explained on the basis of severe spasm of a large coronary artery as its cause The attack occurs at rest because myocardial oxygen consumption is reduced and coronary vasoconstriction develops during rest In addition the increased activity of the vagus nerve which occurs during rest[19] is believed to stimulate the sympathetic nerve to release norepinephrine which in turn activates alpha adrenergic receptors in the large coronary artery The attack does not occur during exercise because myocardial oxygen consumption is increased and coronary vasodilatation develops An ST segment elevation in the ECG occurs during the attack because severe spasm develops at a large coronary artery and it is documented that temporary occlusion of a large coronary artery causes ST segment elevation without infarction

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In four patients with Prinzmetal's variant form of angina the attack was induced by the combined administration of epinephrine (0 4 to 0 5 mg given subcutaneously at 7 30 to 8 00 A M) and propranolol (40 mg given orally at 5 00 A M) Selective coronary cinearteriography was done before during and after the attack with constant monitoring of the ECG and blood pressure

Severe spasm of the right coronary artery

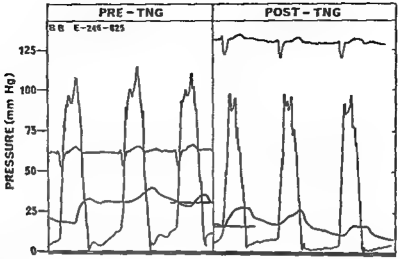

Fig. 1. Hemodynamic effects of TNG in a patient with mitral stenosis. Control left ventricular and left atrial pressure tracings and ECG are at left. Five minutes after administration of 0.3 mg of TNG there was a reduction in both left atrial and left ventricular pressures without a change in heart rate. Mean left atrial pressure, represented by the horizontal bars, decreased from 30 mm Hg before TNG to 15 mm Hg after TNG.

glycerin caused a decrease in pulmonary and systemic pressures in all patients. An example of the effect of TNG upon these pressures is shown in Fig. 1. While the effects of TNG were maximal at 5 to 7 minutes, pressures remained below control levels for at least 20 minutes. Observations for longer than this time period were not made.

Phasic and mean pulmonary artery pressures, mean left atrial pressure, and left ventricular systolic and end diastolic pressures all fell significantly with TNG (Fig. 2). For the group, there was no change in heart rate or cardiac index; however, stroke index fell slightly (Table I). With respect to mitral valve measurements, the mitral valve gradient decreased (Fig. 2), but mitral valve flow, diastolic filling period, and mitral valve area measurements did not change (Table I). The pulmonary vascular resistance decreased for the group; however, the fall in PVR was significantly greater ($p < 0.05$) in patients with an elevated resting PVR (> 2.2 RU) than in patients with a normal resting PVR (≤ 2.2 RU).

On an individual basis there was a strong positive correlation between the decrease in mean LA pressure and the decrease in pulmonary pressures (Fig. 3). On the other hand, there was no significant correlation between the decrease in LV systolic or end diastolic pressure and the decrease in LA pressure. While there was no group change in heart rate, cardiac index, mitral valve gradient, or mitral valve flow, a decrease in each of these variables correlated with a decrease in LA pressure (Fig. 3).

Discussion

As early as 1910, William Osler recognized that symptoms of pulmonary congestion often accompanied angina pectoris. He commented that both the anginal pain and the associated respiratory symptoms were relieved by amylnitrate.[8] In 1924, Gallavardin[9] noted that nitroglycerin also relieved the dyspnea of angina pectoris. While previous investigations have focused upon the efficacy of TNG in relieving pulmonary vascular congestion in conditions characterized by left ventricular failure,[1] the present study has demonstrated that TNG is effective in lowering pulmonary pressures in mitral stenosis in the absence of left ventricular failure.

In mitral stenosis, the pulmonary venous or left atrial pressure is directly related to mitral valve flow; thus an elevation of pulmonary venous pressure is required to increase the mitral valve flow rate.[1] Conversely, pulmonary venous pressure may be lowered in mitral stenosis by either a reduction of mitral valve flow rate and therefore mitral valve gradient or a reduction in left ventricular diastolic pressure with no change in the mitral valve gradient.

The effect of nitroglycerin upon pulmonary and left atrial pressures in patients with mitral stenosis

Donald A Rothbaum, M D
James C Dillon M D
Harvey Feigenbaum, M D
Indianapolis Ind

In addition to nitroglycerin's effectiveness in alleviating the pain of angina pectoris the drug usually relieves the respiratory distress which often accompanies this syndrome In conditions such as angina pectoris[1-3] acute myocardial infarction[4] and hypertensive cardiovascular disease, nitroglycerin has been shown to decrease pulmonary artery and pulmonary capillary wedge pressures Since nitroglycerin effectively lowers pulmonary pressures in patients with left ventricular failure, it was felt that the drug might alleviate pulmonary vascular congestion in patients with mitral stenosis, a condition characterized by elevated pulmonary pressures without left ventricular failure In an evaluation of nine patients with mitral stenosis it was found that the hemodynamic response to nitroglycerin was a consistent fall in pulmonary artery and left atrial pressures irrespective of changes in heart rate or cardiac output

Methods

Hemodynamic studies were performed in nine patients undergoing cardiac catheterization for predominant mitral stenosis The average age of the patients was 45 years The cardiac rhythm was normal sinus in four patients and atrial fibrillation in five patients Four of the five patients with atrial fibrillation were taking digitalis at the time of the study None of the patients had evidence of left ventricular failure Valvular lesions, other than mitral stenosis, were all considered mild Pulmonary artery (PA) pressure was recorded through a Goodale Lubin catheter left atrial (LA) pressure was recorded through a transseptal Brockenbrough catheter, and left ventricular (LV) pressure was recorded through a retrograde aortic catheter Cardiac output (CO) was measured by the Fick oxygen consumption technique with PA and LV blood samples drawn simultaneously during a 4 minute breathing collection PA LA, and LV pressures were recorded during the CO determination After completion of the control CO and pressure measurements 0 4 mg of nitroglycerin (TNG) was given sublingually At the time of peak TNG effect (between 5 and 7 minutes after administration) the CO and pressure measurements were repeated Pulmonary vascular resistance (PVR) in resistance units (RU) was calculated by the formula (mean PA pressure − mean LA pressure)/CO Mitral valve gradient was estimated by planimetry Mitral valve area was calculated by the Gorlin formula mitral valve flow/(31 × square root of mitral valve gradient)[5]

Student's t test and linear regression analysis for paired and unpaired data were used for all statistical comparisons

Results

The clinical and hemodynamic data for the nine patients are summarized in Table I Nitro

From the Krannert Institute of Cardiology and the Department of Medicine Indiana University School of Medicine Indianapolis Ind

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Reprint requests Donald A Rothbaum M D Indiana University Medical Center 1100 W Michigan St Indianapolis Ind 46207

MPA	Δ	LA	Δ	PVR	Δ	MVG	Δ	MVA	DFP	Δ	MVF	Δ
(mm Hg)		(mm Hg)		(U)		(mm Hg)		(cm)	(sec /min)		(ml /DF sec)	
47	−29	30	−15	4 1	−3 4	24	−11	0 8	35.5	+1.5	121	−7
18		15		0 7		13			37 0		114	
41	−2	26	− 3	3 4	−0 2	15	0	1 0	37 4	−1 1	118	+17
39		23		3 2		15			36 3		135	
46	−9	28	−4	5 8	−1 6	13	[illegible]	0 8	34 7	−0 7	83	+2
37		24		4 2		13			34 0		91	
74	−19	25	−7	21.3	−1 9	17	−4	0 7	28 6	+3 4	82	−23
55		18		19 4		13			32 0		59	
65	−27	42	−17	3.5	−1 6	32	−10	1 6	28 1	+0 7	278	−45
38		25		1 9		22			28 8		233	
26	−11	16	−8	2 1	−0 2	9	−2	1 6	31.9	−0 9	151	−36
15		8		1 9		7			31 0		115	
47	−8	34	−6	2 2	−0 2	23	−6	1.3	29 7	−1 3	199	−5
39		28		2 0		17			28 4		194	
22	−8	16	−7	1 4	−0 2	10	−3	1.3	34.5	−3 5	125	+11
14		9		1 4		7			31 0		136	
[illegible]6	−30	36	−13	8 3	−2 1	31	−3	0 8	34 4	+1.3	139	−35
46		23		6 2		28			35 7		104	
49	−15 9	28	−8 9	5 8	−1 3	19	−4 3	1 1	32 8	−0 1	145	−14
33	± 3 7	[illegible]	±1	4 5	± 4	15	±1.3	± 1	32 7	±0 7	131	±7
	< 0 005		< 0 001		< 0 025		< 0 01			NS		NS

accounted for approximately half of the observed [illegible] mm Hg decrease in mean LA pressure Particularly in the three patients (W B D S D W) who responded to TNG with a marked increase in heart rate (> 15 beats per minute) the fall in LA pressure was due exclusively to the fall in LV diastolic pressure

The remainder of the decrease in mean LA pressure was attributable to a mean reduction of 4.3 mm Hg in the mitral valve gradient While there was no significant mean reduction in the determinants of mitral valve gradient in response to TNG there was a significant individual correlation between a decrease in left atrial pressure and a decrease in cardiac index heart rate and mitral valve flow (all $p < 0.05$) Thus the individual combinations of the effects of TNG upon left ventricular filling pressure heart rate cardiac index and mitral valve flow was such that left atrial pressure fell in all patients studied

Because of its profound effect upon pulmonary pressures nitroglycerin may have altered the

Table I Clinical and hemodynamic data*

Pt	Rhy	HR (beats/min)	Δ	CI (L/min/M²)	Δ	SI (L/min/M²)	Δ	LV (mm Hg)	Δ	PA (mm Hg)	Δ
B B	AF										
C		96	−10	2.5	0	26	+3	112/10	−22/−3	83/29	−50 1
TNG		86		2.5		29		90/7		33/1?	
W B†	SR										
C		55	+19	2.6	+0.3	47	−8	110/12	−12/−5	59/29	−6
TNG		74		2.9		39		98/7		53/24	
D F	AF										
C		68	0	3.1	0	46	0	149/13	−2/−3	72/30	−22 −6
TNG		68		3.1		46		147/10		50/24	
K L	SR										
C		88	+6	1.3	−0.2	15	−3	127/10	−12/−4	108/49	−38/ 9
TNG		94		1.1		12		115/6		70/40	
M I†	SR										
C		134	−14	4.0	−0.6	30	−2	139/5	−5/−1	93/46	−43
TNG		120		3.4		28		124/4		50/26	
D S	SR										
C		84	+16	2.5	−0.5	30	−10	147/12	−32/−6	39/22	−14 11
TNG		100		2.0		20		115/6		25/11	
D W	AF										
C		110	+25	3.2	−0.2	29	−7	123/13	−9/−5	66/35	−15 11
TNG		135		3.0		22		114/8		51/29	
O W	AF										
C		80	0	2.3	0	29	0	121/8	−14/−4	37/16	−17/−5
TNG		80		2.3		29		107/4		20/11	
F Z†	AF										
C		86	+8	2.7	−0.6	31	−9	155/7	−22/−6	115/50	−42/ 13
TNG		94		2.1		22		133/1		73/3?	
Mean											
C		89	+5.6‡	2.7	−0.2	31	−4.0	131/10	−15.6 ± 2.8	74/34	−6.9 ± 5.9
TNG		94	±4.4	2.5	±0.1	27	±1.6	116/6	−4.1 ± 0.9	47/24	−10.2 ± 1.9
P			NS§		NS		< 0.05		< 0.001/ < 0.001		< 0.005/ < 0.001

Abbreviations C control before TNG TNG after nitroglycerin Rhy cardiac rhythm AF atrial fibrillation SR sinus rhythm HR heart rate CI cardiac index SI stroke index LV left ventricular pressure PA pulmonary artery pressure MPA mean PA pressure LA mean left atrial pressure PVR pulmonary vascular resistance MVG mitral valve gradient MVA mitral valve area DFP diastolic filling period MVF mitral valve flow NS p value not significant

†Mild aortic insufficiency

‡Mean ± S E of paired differences

§ P value of difference

In this study, nitroglycerin appeared to exert its beneficial effect by a combination of several hemodynamic alterations As shown by several investigators, nitroglycerin is a potent vasodilator affecting both the arteriolar and venous systems [12-14] Nitroglycerin reduced not only systemic and pulmonary arterial pressures but also left ventricular filling pressure in all patients in our study

For the group the 4 mm Hg decrease in left ventricular end diastolic pressure which corresponds quite closely to the decrease in left ventricular mean diastolic pressure in patients with mitral stenosis and no appreciable a wave

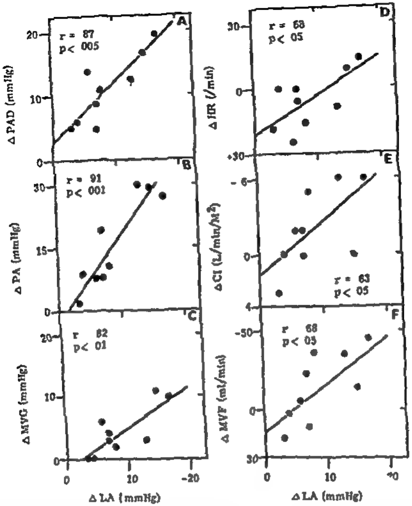

Fig 3 Correlation between the decrease in selected hemodynamic variables and the decrease in mean LA pressure In response to TNG administration the magnitude of the fall in mean LA pressure was significantly correlated with the fall in PA diastolic pressure (PAD) PA mean pressure MVG heart rate (HR) cardiac index (CI) and mitral valve flow (MVF)

pulmonary vascular resistance The decrease in left atrial pressure was attributable to the combination of a reduction in left ventricular filling pressure and a reduction in mitral valve gradient While there was no significant mean change in heart rate cardiac index or mitral valve flow there was a significant correlation between a decrease in each of these determinants of mitral valve gradient and the observed decline in left atrial pressure in individual patients However even those patients who had an increase in heart rate or cardiac output either of which normally aggravates pulmonary congestion in mitral stenosis had a decrease in their pulmonary and left atrial pressures in response to TNG It is likely that nitroglycerin reduced pulmonary and left atrial pressures by either (1) systemic venous dilatation causing a reduction in right heart filling and pulmonary blood volume or (2) pulmonary arteriolar and venous dilatation causing a decrease in pulmonary vascular resistance and an increase in pulmonary vascular compliance Because of the efficacy of TNG in lowering pulmonary and left atrial pressures in this study TNG may prove useful in the clinical management of symptomatic pulmonary congestion in mitral stenosis

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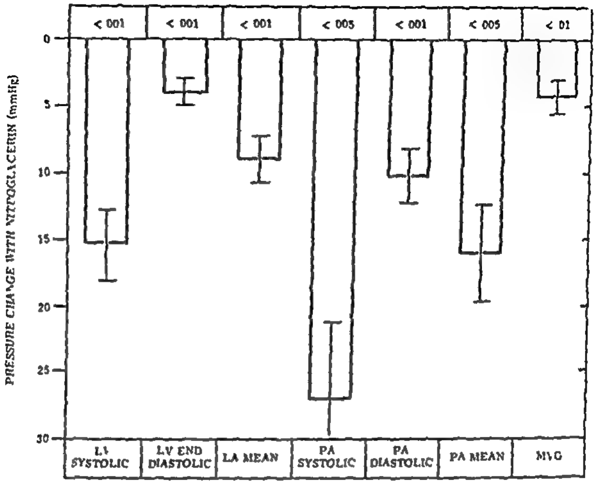

Fig 2 Effect of TNG upon LV LA and PA pressures and upon MVG Pressure decrease is expressed as mean ± SE with the respective p value above the bar

pressure volume characteristics of the pulmonary circulation In studies of the pathophysiology of pulmonary congestion it has been demonstrated that pulmonary vascular compliance is reduced[11 18] Consequently either a decrease in pulmonary blood volume or a relaxation of pulmonary venomotor tone would result in a reduction in pulmonary pressures By its ability to cause peripheral pooling of blood, TNG causes a reduction in right heart filling pressure[9 19] As a result pulmonary blood volume may decrease and pulmonary pressures would then decrease without the necessity for an actual change in pulmonary vascular compliance On the other hand TNG may have a direct effect upon the pulmonary vasculature to decrease pulmonary venomotor tone and lower pulmonary pressures Brachfeld and associates[19] suggested that TNG caused a relaxation of pulmonary venomotor tone in both normal subjects and patients with mild cardiac disease In an animal preparation with a left heart bypass to prevent the systemic effects of TNG, Pinkerson and associates[9] showed that TNG had a direct effect on the pulmonary circulation causing a consistent decrease in pulmonary vascular resistance Ferrer and associates[1] observed that pulmonary blood volume increased but pulmonary pressures fell after nitroglycerin their study suggests that pulmonary vascular resistance decreased and compliance increased after TNG

In our study the three patients with a normal resting PVR (≤ 2 2 RU) had only a minimal fall in PVR with TNG (−0 2 RU) In contrast five of the six patients with an elevated PVR at rest had a marked fall in PVR with TNG (range −1 6 to −3 4 RU) the only exception was a patient (W B) with pulmonary hemosiderosis by chest x ray Thus TNG appeared to be most effective in reducing pulmonary vascular resistance in cases in which it was pathologically but reversibly elevated at rest

Summary

In all nine patients studied with mitral stenosis and no evidence of left ventricular failure nitroglycerin caused a decrease in pulmonary arterial left atrial, and left ventricular pressures and

Electroencephalographic study in acute rheumatic carditis

Ali Ertugrul M D
Yavuz Renda M D
Muhsin Saraciar M D
Mine Oner M D
Sezer Akay M D
Ankara Turkey

In the last century various authors have written about the presence of vascular and cerebral changes due to endarteritis found during the autopsy of rheumatic cases[1] In all these autopsies rheumatic patients who had endarteritis also had some lesions of rheumatic carditis

Electroencephalographic (EEG) studies of rheumatic fever were done in cases of Sydenham s chorea in 1941 and later in other types of rheumatic disease Nyman[2] Lavy and associates[3] Oner Ozturk[4] Sezer[5] and Renda and associates showed that EEG changes can be seen in rheumatic fever patients without neurologic symptoms

Our preliminary studies gave the impression that EEG changes were consistent with active carditis and that the EEG returned to normal when the disease subsided

This study has been planned in order to answer the following questions (1) How often can EEG changes be seen in rheumatic fever patients who do not have neurologic findings? (2) What is the frequency of EEG changes in acute polyarticular rheumatic fever without carditis? (3) What is the frequency of EEG changes in rheumatic carditis? (4) Are the EEG changes related to rheumatic activity? (5) What is the correlation if any between the sedimentation rate and tachycardia in EEG changes? (6) How long do the EEG changes continue? (7) Finally can the EEG changes be a criterion for the determination of the activity in rheumatic carditis?

Material and methods

Cases in this study were selected from patients who were admitted to the Pediatric Cardiology Unit of the Hacettepe University Children s Hospital between 1971 and 1973 There were 1,243 rheumatic fever patients and 60 per cent of these were our regular follow up cases The age range was between 7 and 16 years, the sex distribution was almost identical Of these cases we selected 30 patients with acute polyarticular rheumatic fever without carditis 25 with inactive rheumatic heart disease 25 with acute active rheumatic carditis and 85 with Sydenham s chorea The last 25 acute active rheumatic carditis cases were followed until EEG changes returned to normal The history of the present disease and the past history of rheumatic fever were carefully noted Complete physical (including neurologic) examinations were done Patients with neurologic findings were excluded from this study and also patients with a definite or suspected history of epilepsy

Another 43 children from the outpatient clinic with no signs of rheumatic collagen or neurologic disease were matched for age and sex and used as a control group (Table I) 85 patients with definite findings of Sydenham s chorea were also chosen as a second control group

Only those patients with all the following findings were considered as having active rheumatic carditis tachycardia in sleep joint symptoms significant murmurs increased heart size

From the Pediatric Cardiology Unit Children s Hospital Hacettepe Medical School, Hacettepe University Ankara Turkey

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Reprint requests A. Ertugrul M D Professor of Pediatrics and Head of the Pediatrics Cardiology Unit, Hacettepe Medical School Children Hospital, Ankara, Turkey

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Ali Ertugrul, M.D.
Yavuz Renda, M.D.
Muhsin Saracıar, M.D.
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Sezer Akay, M.D.
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From the Pediatric Cardiology Unit, Children's Hospital, Hacettepe Medical School, Hacettepe University, Ankara, Turkey.

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Reprint requests: A. Ertugrul, M.D., Professor of Pediatrics and Head of the Pediatrics Cardiology Unit, Hacettepe Medical School, Children's Hospital, Ankara, Turkey.

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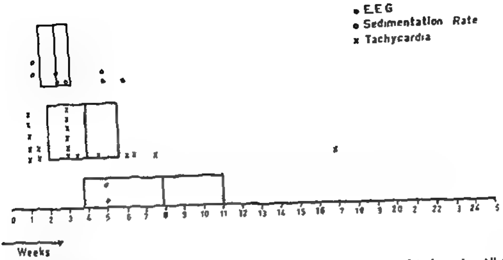

Fig 3 Comparative durations of abnormalities of EEG high sedimentation rate and tachycardia All these patients were under corticosteroid treatment in the hospital The mean duration for returning to normal was about 16 days for sedimentation rate 4 weeks for tachycardia and 8 weeks for EEG abnormality

Table I EEG studies in 208 cases of rheumatic fever

Acute active rheumatic carditis		*Inactive rheumatic valvular heart disease*		*Polyarticular rheumatic fever*		*Sydenham s chorea*		*Control group*	
No of cases	*Abnormal EEG*	*No of cases*	*Abnormal EEG*	*No of cases*	*Abnormal EEG*	*No of cases*	*Abnormal EEG*	*No of cases*	*Abnormal EFG*
25	24 96%	25	3 12%	30	2 6 6%	85	23 27%	[illegible]	6 14%

a minimum of two and a maximum of nine tracings These patients were followed for a period which ranged from 2 to 22 weeks (see Figs 1 and 2)

Out of 25 patients with active acute rheumatic carditis 24 had abnormal EEG s (94 per cent) All showed rhythm abnormalities and 10 had a marked voltage suppression (Table I)

The rate of EEG abnormality from the 43 control patients was 14 per cent compared with 27 per cent found in 23 of the 85 patients with Sydenham s chorea

Only two of 30 acute rheumatic polyarthritis patients had abnormal EEG changes (6 6 per cent)

As shown in Fig 3 EEG tracings returned to normal after approximately 8 weeks whereas the sedimentation rate returned to normal within 2½ weeks and tachycardia within 4 weeks

Of the 25 active carditis patients with rhythm abnormalities of EEG 21 returned to normal Three patients did not appear for EEG controls Four of 10 patients who had diffuse voltage suppression had completely normal voltage on the last tracing

Of the 25 patients with inactive rheumatic heart disease there was only one who had rhythm disturbance in his EEG Of 30 patients with acute polyarticular rheumatic fever without carditis there were only two with rhythm abnormalities and one with low voltage

Discussion and conclusion

EEG abnormalities have been noted in patients with Sydenham s chorea since 1941 During the last three decades EEG abnormalities have been found in rheumatic fever patients without Sydenham s chorea and without any neurologic findings On the other hand Diamond[2] found no EEG abnormalities in rheumatic patients without

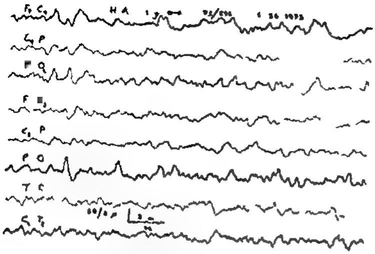

Fig 1 First EEG tracing of an active rheumatic carditis patient showing definite slow and sharp wave abnormalities over all brain regions

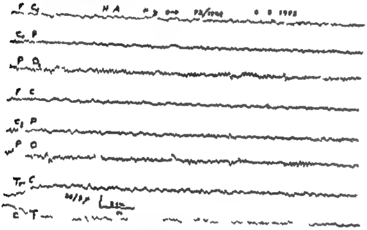

Fig 2 Fourth EEG (same patient as in Fig 1) after 9 weeks shows complete normalization of the tracing

fever of 37° C and over elevated sedimentation rate and increased ASO titer (Only three of these patients had a temperature under 37° C and only one patient s ASO titer was less than 300 U there was only one patient with heart failure who had a normal sedimentation rate on admission)

Eleven of 25 patients had heart failure, 10 patients had pure MI five had MS + MI, six had MI + AI two had MI + MS + AI one had MS + TI one had MS + AI + TI

Patients with active carditis had been hospitalized for 4 weeks or more All hospitalized patients were kept at bed rest

Corticosteroids penicillin and if necessary anticongestive treatment for heart failure were given

The first EEG s were obtained on the first day of admission and the second EEG s 7 to 10 days later Further EEG's were taken every 15 to 20 days while the patient was in hospital and every 30 days after discharge, until the EEG rema ed normal in two consecutive readings

In the inactive rheumatic heart disease group (25 cases) only those patients with definite rheumatic valvular disease (but who did not show any changes other than normal variation at least during the last year, in their sedimentation rate ASO titer, pulse rate, heart size, murmurs EEG and x rays) were included

There was no significant difference in the severity of heart lesions in the two groups, although there were a few more heart failure patients in the active rheumatic heart disease group Three of the 25 nonactive rheumatic carditis patients had heart failure, 11 had MI, one had MS, three had AI, five had MI + MS two had MS + AI one had MI + MS + AI

The EEG's were obtained by Grass VI Eight channel apparatus and 19 20 international electrode system was used Two interpreters analyzed the recordings by the double blind method without knowing from which groups the patients came or their diagnoses

Abnormalities were classified as follows

1 Changes in the background activity were grouped as
   - Focal slow and sharp waves in 4 to 6 c p s frequency Localization of these waves was inconsistent in each tracing
   - Diffuse slow waves in 3 to 7 c p s frequency These were more pronounced on the posterior head regions and quite irregular
   - Paroxysmal sharp waves in 3 to c p s frequency There were no definite foci for these
   - Loss (or paucity) of alpha rhythm in many tracings

2 There was diffuse voltage suppression in most of the recordings, but this finding was thought to be inconclusive
   - The abnormalities were continuous and not consistent with the eye opening or closing
   - Hyperventilation and photic stimulation did not induce marked changes in any of these tracings
   - None of the patients showed marked drowsiness or slept during the recordings

Findings

There were 137 tracings of 25 patients with active acute rheumatic carditis Each patient had

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chorea Nyman[11] noticed that EEG abnormalities in active rheumatic fever returned to normal after the signs of activity disappeared

In this study we divided our rheumatic fever patients into three groups (1) acute polyarthritis without carditis (2) acute active carditis and (3) nonactive old rheumatic valvular heart disease

An earlier study concerned with EEG findings in Sydenham's chorea cases[12] in this institution showed an abnormality rate of 27 per cent

This study demonstrated that involvement of the central nervous system in acute rheumatic carditis is more common than is generally believed Although clinical examination of patients did not show any neurologic deficit the EEG's almost always demonstrated abnormalities in acute carditis

The incidence of abnormal EEG's in nonactive rheumatic valvular heart disease and polyarticular rheumatic fever without carditis is not higher than the abnormal EEG's found in normal persons

In this study patients with definite active carditis and nonactive old rheumatic heart disease were selected from several hundred rheumatic patients

The EEG's of 21 follow up cases with active rheumatic carditis returned to normal within 3 to 23 weeks

We can assume that anatomical changes of the central nervous system could be the cause of EEG changes and normalization of the EEG findings can be attributed to the improvement of the original lesion in the central nervous system

When the EEG abnormalities are compared with the other signs of activity of rheumatic fever, such as sedimentation rate and pulse rate, EEG abnormalities would seem to be a more persistent indication of activity of rheumatic fever

Fig 3 shows that the sedimentation rate returns to normal within 4 weeks and the EEG returns to normal within 8 weeks in all the patients under corticosteroid treatment We have not tried to determine the duration of EEG abnormalities in acute active carditis patients who did not have corticosteroid treatment

One could assume from the above findings that corticosteroid treatment is not effective enough to change the EEG abnormalities If the EEG abnormality is an important indicator of the rheumatic activity, it is conceivable that the normalization of the EEG could be a more reliable laboratory finding in determining the long range recovery process of active rheumatic carditis Another study in our department revealed that Australia antigen was also positive in 40 per cent of acute rheumatic cases[4]

All these observations suggest that the pathogenesis may be different in two clinical types of rheumatic fever Migratory polyarticular rheumatic fever without carditis may be due to only poststreptococcal reaction, whereas for rheumatic carditis an additional cofactor seems to be necessary In active carditis the presence of Australia antigen and abnormality of the EEG are strongly suggestive of the presence of such a cofactor in rheumatic cases This cofactor might be a viral infection during or prior to streptococcal infection as was suggested by Burch and his colleagues[19]

It is obvious that this problem requires further investigation

Summary

Electroencephalographic studies were done in rheumatic fever patients in order to determine the distribution of normal and abnormal EEG patterns in different clinical forms The duration of EEG abnormalities related to rheumatic activity was compared with the duration of increased sedimentation rate and tachycardia

Rheumatic fever cases were divided into four groups (1) acute active rheumatic carditis (2) acute polyarthritis without carditis (3) nonactive old rheumatic valvular heart disease and (4) Sydenham's chorea

EEG findings were within normal limits in acute polyarthritis and in nonactive rheumatic valvular heart disease but there were abnormal EEG findings in 29 per cent of chorea and in 94 per cent of active carditis cases

In active carditis all EEG changes returned to normal approximately within 8 weeks whereas the sedimentation rate and tachycardia returned to normal within a shorter period

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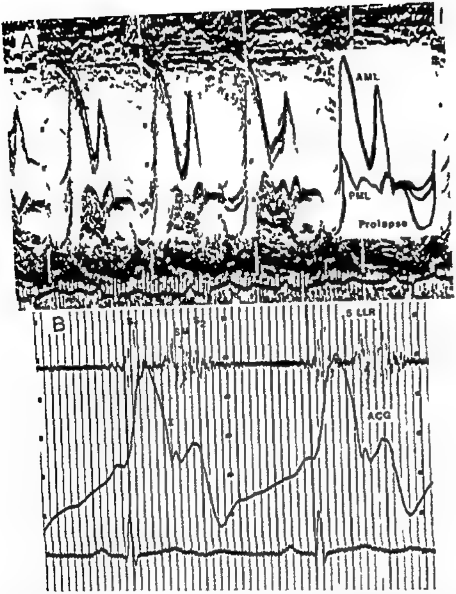

Fig 1 *A* Echocardiogram of a tall 47 year old woman with a 30 year history of a heart murmur and recent episodes of anterior chest pain Other than the auscultatory abnormalities this patient was noted to have a high arched palate and mild cardiomegaly The echocardiograph demonstrates prolapse of both the anterior (*AML*) and posterior (*PML*) mitral leaflets. The complex on the right has been traced to emphasize the abnormal features The prolapse begins in midsystole and therefore is Type A A reduplicated echo from the prolapsing anterior leaflet probably represents redundant leaflet tissue *B* Phonocardiogram recorded minutes before the echocardiogram in (*A*) and identical to other sound tracings recorded simultaneously with the echogram Both the phonocardiogram and apexcardiogram (*ACG*) were registered in the fifth left intercostal space with the patient in the left lateral recumbent (*LLR*) position A prominent midsystolic click (X) precedes a loud late systolic murmur (*SM*)

slightly rotated to the left to enable optimal echocardiographic examination Echocardiographic information was displayed on a multichannel oscillographic recorder (Kent Cambridge Instrument Co Ossining N Y) and permanent photographic records were obtained with a strip chart recorder A simultaneous electrocardiographic Lead II was also continuously recorded

Phonocardiograms were recorded with a piezo electric crystal microphone (Type 53616 Kent Cambridge) with a frequency range of 30 to 600 cps positioned sequentially along the left sternal border and at the site of apical impulse or in the fifth left intercostal space at the midclavic

Double mitral leaflet prolapse
Echocardiographic-phonocardiographic correlation

Michael V Cohen, M D
Bronx N Y

Since the original description of the mitral valve prolapse syndrome in 1963[1] many reports have documented the clinical characteristics of this distinctive valvular lesion The combination of midsystolic click and late systolic murmur has come to be recognized as the typical auscultatory findings in patients with abnormalities of the suspension apparatus of the mitral valve[2-…] These findings are sufficiently distinctive to indicate the diagnosis before invasive studies are performed However less typical auscultatory findings have more recently been described namely, isolated systolic clicks[…] and nonspecific pansystolic murmurs[…] Some patients with documented mitral valve prolapse have even had normal cardiac examinations[17, 18, 23] thus making the clinical diagnosis more elusive The angiographic appearance of the prolapsing mitral valve has failed to account for these diverse auscultatory events However, left ventriculography does not easily define anterior leaflet prolapse Additionally a recent report suggests that studies which have claimed documentation of prolapse of this leaflet may have been in error[…] Therefore the introduction of echocardiography has been invaluable Not only does ultrasound study provide a powerful diagnostic tool which can detect abnormal mitral motion irrespective of the patient's clinical presentation, but it can also define disease of the anterior leaflet Although the report of Dillon and associates[17] demonstrated the ability of the echocardiogram to diagnose prolapse of both anterior and posterior leaflets most echocardiographic studies and comprehensive reviews have focused on prolapse of only one—usually the posterior—leaflet[…] Thus evaluation of the incidence or significance of anterior or double mitral leaflet involvement has been lacking Recently DeMaria and associates[…] presented the variable spectrum of echocardiographic findings in patients with this syndrome and suggested that combined prolapse of anterior and posterior mitral leaflets was quite common The present study documents simultaneous prolapse of both mitral leaflets in a significant percentage of the examined patient population and supports the observations of DeMaria and associates[…] Furthermore despite selection of a more homogeneous patient group with obvious prolapse of both mitral leaflets a variety of auscultatory abnormalities continues to be evident The pathophysiologic understanding of the genesis of the sounds and murmurs in this syndrome continues to be unclear

Methods

All patients studied were referred to the noninvasive laboratory of Montefiore Hospital and Medical Center for diagnostic evaluation Approximately one half of the patients were referred by private practitioners because of the detection of a cardiac murmur or abnormal sound The remaining patients were referred by the house staff as part of a routine work up prior to cardiac catheterization All echocardiographic studies were performed with a Hoffrel Ultrasonoscope Model 101, and either a 2 25 MHz transducer focused at 7 5 cm or an unfocused 2 0 MHz transducer The patient was either supine or

From the Division of Cardiology Montefiore Hospital and Medical Center and the Albert Einstein College of Medicine Bronx N Y

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Reprint requests Michael V Cohen M D Department of Cardiology *Montefiore Hospital and Medical Center* 111 E 210 St Bronx N Y 10467

Results

Of the 347 patients referred for evaluation of murmurs and abnormal sounds the echocardiographic diagnosis of mitral valve prolapse was made in 35 patients If both mitral leaflets in the patients with prolapse could not be definitely identified in systole the prolapse was considered to represent involvement of only one leaflet Nineteen of these 35 echocardiograms clearly demonstrated prolapse of both the anterior and posterior leaflets Nine of these subjects were female with a mean age of 26 1 years (range 14 to 46) and 10 were male with an average age of 39 8 years (range 14 to 69) Of the 19 patients five had the clinical diagnosis of Marfan s syndrome Two of these five patients were identical twins and the mother of a third patient also had double mitral leaflet prolapse One patient had a straight back syndrome without any other apparent cardiac abnormality while another patient had an atrial septal defect with a 2 5 1 left to right shunt The remaining 12 patients were not thought to have other cardiac lesions Three of this group of 19 patients had left ventriculography at the time of cardiac catheterization Prolapse of both anterior and posterior mitral leaflets could be confirmed in two of these patients anterior leaflet prolapse could not definitely be documented in the third

As suggested by Shah and Gramiak two forms of prolapse were recognized The more common form Type A was documented in 13 of the 19 patients Fig 1 *A* shows an example of this abnormality At end diastole the anterior and posterior leaflets coapt and remain apposed for the initial one third to one half of systole The motion is generally horizontal or slightly anterior as is seen in normal mitral valve echograms There is then an abrupt posterior sagging of both leaflets The posterior leaflet in this patient is seen to almost touch the left atrial wall

The second type of double leaflet prolapse Type B is exemplified in Fig 2 *A* In this echocardiogram both leaflets are noted to move posteriorly after meeting at the end of diastole and remain in this abnormal position until the beginning of the following diastolic phase This pattern was observed in 6 of the 19 patients

There was no apparent correlation between the echocardiographic and phonocardiographic findings As noted in Table I five of the patients with Type A and two with Type B prolapse had the classical auscultatory syndrome of a midsystolic click followed by a late systolic murmur An example of this syndrome in a patient with Type A prolapse is seen in Fig 1 *B* One additional patient with a Type A pattern had an isolated midsystolic click (Fig 3) Holosystolic murmurs were heard in three patients with midsystolic and two with pansystolic prolapse Clicks if present were obscured by the long loud murmur In one patient (Fig 2 *B*) the murmur ended shortly before the second sound and a loud late systolic click was obvious Curiously one patient with Type A prolapse had no clinical cardiac abnormalities This patient was a 14 year old boy with a Marfanoid body habitus who was being evaluated because of an intermittently audible murmur His echocardiogram and simultaneous phonocardiogram are seen in Fig 4 *A* At the time of this recording no abnormal sound or murmur could be detected Additionally echocardiographic analysis revealed a normal left atrial dimension His mother (Fig 4 *B*) had virtually identical echocardiographic abnormalities The striking double leaflet involvement with prolapse well into the left atrium is apparent The left atrial dimension was enlarged in this patient A mid to late systolic murmur was easily heard at the apex and the left sternal border but no click was detected. Therefore despite similar mitral valve abnormalities the clinical presentation and

Table I Correlation of echo and phonocardiographic abnormalities in patients with double mitral leaflet prolapse

	No of patients
Late systolic prolapse—Type A	13
Midsystolic click and late systolic murmur	5
Mid to late systolic murmur with late increase in intensity	3
Pansystolic murmur	2
Pansystolic murmur with late increase in intensity	1
Isolated click	1
Normal	1
Pansystolic prolapse—Type B	6
Midsystolic click and late systolic murmur	2
Long systolic murmur and late systolic click	1
Late systolic murmur	1
Pansystolic murmur	2

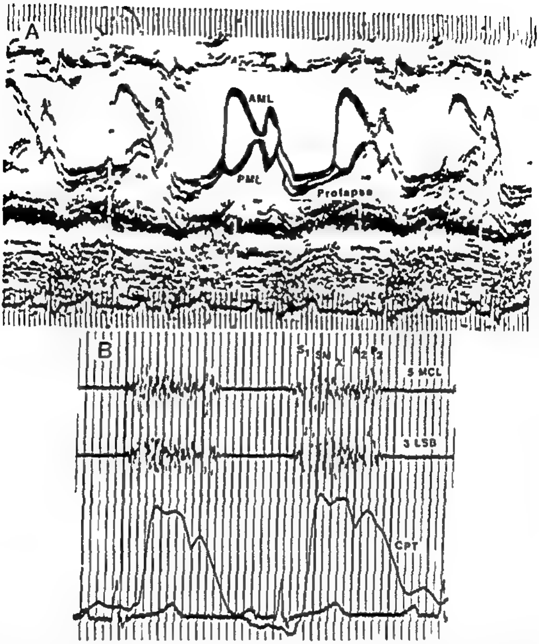

Fig 2 *A* Echocardiogram of a 43 year old asymptomatic man with cardiac enlargement noted on routine chest x ray done for tuberculosis screening Physical examination was compatible with the diagnoses of atrial septal defect and mitral regurgitation At the time of cardiac catheterization the patient had a 2 5 1 left to right shunt at the atrial level moderate mitral regurgitation and prolapse of both mitral leaflets The echocardiogram demonstrates prolapse of both the anterior (*AML*) and posterior (*PML*) mitral leaflets As can be best seen in the artist's redrawing of one of the complexes the two leaflets meet at end diastole and then immediately sag posteriorly This pansystolic prolapse pattern is Type II *B* Phonocardiogram of this patient recorded along the left sternal border in the third left intercostal space (*3 LSB*) and at the midclavicular line in the fifth intercostal space (*5 MCL*) showing a prominent early to midsystolic murmur (*SM*) Although long the murmur does not obscure a mid to late systolic click (X) A widened A_2 P_2 interval is also appreciated The carotid pulse tracing (*CPT*) is superimposed for purposes of timing

ular line These tracings were recorded either simultaneously with or immediately before the echocardiographic studies in all patients Reference carotid pulse tracing and apexcardiogram were also recorded with piezoelectric crystal transducers (Types 53642 and 72453, Kent Cambridge)

Available catheterization studies of patients with the echocardiographic diagnosis of mitral valve prolapse were reviewed Angiography was done less than 24 hours after the noninvasive studies Biplane left ventricular cineangiography was performed in each patient in the right and left anterior oblique projections and 35 mm film was used to record the motion of the opacified ventricle at a rate of 50 frames per second

Results

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Pansystolic prolapse—Type B	6
Midsystolic click and late systolic murmur	2
Long systolic murmur and late systolic click	1
Late systolic murmur	1
Pansystolic murmur	2

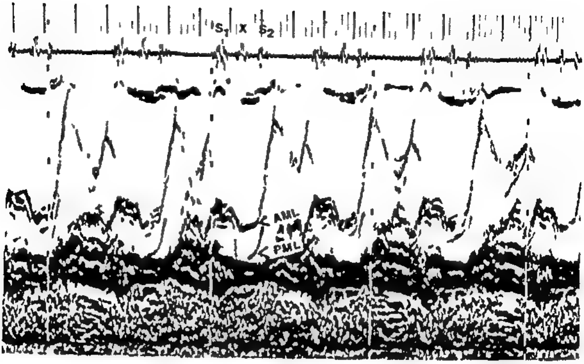

Fig 3 Simultaneously recorded phonocardiogram and echocardiogram of an 11 year old girl referred for evaluation of a midsystolic click (X) No murmur could be detected *The echocardiogram shows Type A prolapse of both mitral leaflets* *AML* = anterior mitral leaflet *PML* = posterior mitral leaflet

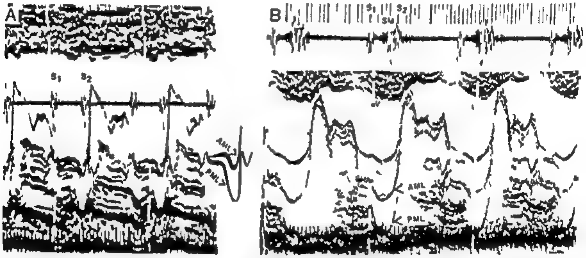

Fig 4 *A* Simultaneously recorded phonocardiogram and echocardiogram of a 14 year old boy with a Marfanoid body habitus Although his private physician had previously heard a systolic murmur both auscultatory and phonocardiographic examinations at the time of this study were unrevealing However the echocardiogram clearly demonstrates Type A prolapse of both mitral leaflets Anterior (*AML*) and posterior (*PML*) leaflet involvement is indicated on the artist's drawing of one of the complexes *B* The 47 year old mother of the patient described in (*A*) Her late systolic murmur (*SM*) is well recorded as is the Type A prolapse of both mitral leaflets

physical signs were significantly different in these two patients A total of four patients three Type A and one Type B had late systolic murmurs without apparent clicks Careful search for these extra sounds was unsuccessful

Discussion

In 1963 Barlow and co workers[1] described a clinical syndrome associated with the striking auscultatory findings of midsystolic click and late systolic murmur In the ensuing 12 years Barlow and others have observed numerous clinical examples of this syndrome [3,30,31] Initial identification was based on clinical and phonocardiographic examination In 1966 Criley and associates[6] pointed out that patients with these physical findings had abnormal motion of the mitral valve leaflets During ventricular contrac

tion the posterior leaflet ballooned or prolapsed into the left atrium causing a characteristic radiologic abnormality Further angiographic study uncovered numerous clinical variant presentations in patients having demonstrable mitral valve prolapse Many series have now documented early systolic clicks[3 29] isolated midsystolic clicks[2 7 9 10 8 19 21 2 2] or late systolic murmurs[11 15 33 34] and even pansystolic murmurs[2 7 1 1 1 1 8 27] In Jeresaty s[7] series of 200 patients with documented mitral valve prolapse only 46 per cent had midsystolic clicks and 11 per cent had nonspecific pansystolic murmurs In this same series 12 per cent had no abnormal clinical findings Thus in at least 23 per cent of Jeresaty s patients the clinical diagnosis of mitral valve prolapse could not have been made

Dinsmore and associates[3] have noted absence of a correlation between the degree of mitral regurgitation location of the prolapse and presence of click and/or murmur However attempts to correlate the numerous auscultatory findings with the angiographic appearance of the abnormal mitral valve have been hampered by the inherent limitations of left ventriculography Most studies have used only the right anterior oblique projection in which the anterior and posterior mitral leaflets are often superimposed Criley and associates initially concluded that prolapse of the posterior leaflet was responsible for the abnormal sounds and many subsequent analyses have confirmed their impression[5 1 11 8 5] Others have claimed documentation of prolapse of both mitral leaflets[13 1 16 19 24 28 3] and two early studies noted isolated prolapse of the anterior leaflet[31] The studies of Ranganathan and associates[30 2] of the normal[1] and prolapsed mitral leaflet however suggest that some of these latter angiograms may have been misinterpreted The posterior leaflet normally consists of a large middle and two smaller flanking scallops[31] Posterior leaflet prolapse may involve one two or all three scallops In the right anterior oblique projection prolapse of the anterolateral commissural scallop causes an anterosuperior bulge in the region of the anterolateral commissure If large this scallop will jut beyond the aortic root Angiographic morphologic correlation in patients in Ranganathan s series identified an abnormal posterior leaflet scallop as the cause of the anterosuperior bulge visualized during left ventriculography This bulge may have been incorrectly interpreted as prolapse of the anterior leaflet in earlier studies Surgical and pathologic specimens have shown abnormalities of both mitral leaflets[34] but radiologic demonstration of anterior leaflet prolapse would depend on additional left anterior oblique projections Because of this difficulty in angiographic interpretation adequate correlations between angiographic and phonocardiographic abnormalities have not been possible

Echocardiography has become an invaluable tool in the evaluation of many cardiac abnormalities In 1971 Dillon and associates[17] documented its usefulness in the diagnosis of mitral valve prolapse Their report also demonstrated the ability of ultrasound to detect prolapse of both mitral leaflets At least one of the patients presented by Burgess and associates[29] had similar findings However until the recent study of DeMaria and associates[21] emphasis in echocardiographic reports was placed on prolapse of only one—usually the posterior—leaflet[2 17 3 22] DeMaria and associates[1] noted that 88 per cent of their patients with ultrasound evidence of mitral prolapse had involvement of both anterior and posterior leaflets The present report has documented double mitral leaflet prolapse in only 61 per cent of the patients This figure is likely to be an underestimate since echocardiographic studies which did not clearly define both leaflets were considered to be representative of single leaflet prolapse Nonetheless it is obvious that double prolapse is a common finding This is not surprising since chordae from each of the two left ventricular papillary muscles insert into both mitral leaflets Degeneration or rupture of primary chordal branches would therefore produce abnormal motion of both mitral leaflets Furthermore the mitral leaflets support each other when coapted during systole Pathologic involvement of one leaflet causing prolapse partially removes this support and probably predisposes to prolapsing of the normal leaflet

As noted by others[14 33] two types of prolapse have been documented Thirteen of 19 patients in the present series had prolapse which was first detected in midsystole whereas the remaining six subjects had leaflets prolapsing immediately after the onset of systole In the series of DeMaria and associates,[2] 57 per cent of those with double leaflet prolapse had the Type B or pansystolic

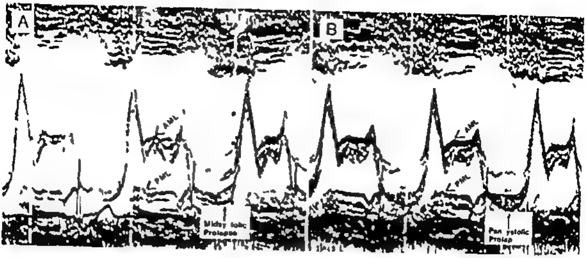

Fig 5 A 21 year old cross country runner who was referred for evaluation of a heart murmur by the team physician *A* Typical echocardiographic features of Type A or midsystolic prolapse of the mitral valve *B* Type B or pansystolic prolapse recorded in the same patient These two echograms were recorded within 5 minutes. There was no obvious change in either the patient s emotional or hemodynamic state The significance of the difference is not apparent Prolapse may be a dynamic abnormality subject to acute and even minor alterations of the individual s cardiovascular state However it is also possible that echocardiographic records of a midsystolic prolapse fail to register the early systolic posterior movement of the leaflet

pattern Although the echocardiographic patterns are readily recognized their significance is unclear In one patient with mitral valve prolapse one tracing of the mitral valve showed Type A (Fig 5, *A*) and the other Type B (Fig 5, *B*) prolapse The two recordings were separated by at most 5 minutes Differentiation of two prolapse types may thus be artificial Or the prolapse may be a dynamic abnormality whose characteristics are dependent upon acute and even transient alterations of the individual patient s cardiovascular state

Other than a cataloguing of echocardiographic and auscultatory abnormalities in this syndrome little attempt has been made to correlate the two Shah and Gramiak[16] noted in their patient population that midsystolic prolapse was associated with the classical findings of midsystolic click and late systolic murmur, whereas pansystolic prolapse was accompanied by a pansystolic murmur In eight patients with isolated systolic clicks Kerber and co workers[20] were unable to detect any echocardiographic abnormalities More recently DeMaria and associates[13] commented on the phonocardiograms done in some of their patients with prolapse and concluded that auscultatory events did not necessarily coincide temporally with mitral prolapse In the present series only patients with double mitral leaflet prolapse have been selected for analysis This more homogeneous group lends more credibility to the derived correlation Correlations in patients with the mitral prolapse syndrome are best done with simultaneously recorded data because of the recognized lability of the auscultatory findings[14] and the possible variability of the echocardiographic abnormalities (Fig 5) Of the 19 patients reported here, 16 had simultaneous echo and phonocardiographic studies, whereas the remaining three patients had phonocardiograms completed minutes before the ultrasound investigations

The diverse auscultatory events from the present series are outlined in Table I It is immediately obvious that the type of prolapse is not associated with any one pattern This observation conflicts with the earlier report of Shah and Gramiak[16] Of particular note is the presence of pansystolic murmurs in three patients considered to have Type A or midsystolic prolapse and mid systolic click and late systolic murmur in two patients with Type B or pansystolic prolapse Contrary to the observations of Kerber and associates[20] prolapse has been documented in the present series in a patient with an isolated midsystolic click (Fig 3) DeMaria and associates[13] have also reported similar findings Jeresaty[24] has concluded that anterior leaflet prolapse whether isolated or combined with posterior leaflet involvement, is infrequently

silent and is usually associated with either a late systolic or pansystolic murmur The observations summarized in Table I suggest a broader range of auscultatory abnormalities in these patients Thus there is no apparent correlation between the echocardiographic and phonocardiographic manifestations of mitral valve prolapse

Explanation of this disturbing conclusion will be elusive until better understanding of the pathophysiologic factors which generate the abnormal sounds is obtained Intracardiac phonocardiography has localized the systolic click and murmur in this syndrome to the region of the mitral valve [10, 7, 40-2] and angiographic analysis has correlated the systolic murmur with the presence of mitral regurgitation [8, 9, 10] In 1961 Reid postulated that the systolic click was caused by a chordal snap Lewis [3] and Dock [4] however have suggested that the leaflets and not the chordae generate the sounds Implicit in the theory that the chordae initiate the click is a postulated midsystolic slackening and subsequent abrupt tensing Although the described ventricular contraction abnormality[23, 25, 27] might displace the papillary muscles and cause this slackening it seems more probable that the chordae become taut at the beginning of systole with the onset of isovolumetric contraction and remain taut as long as the papillary muscles function normally As noted by Rushmer and associates [5] the chordae tendineae and valve leaflets are normally under tension throughout the cardiac cycle Sealing of the mitral valve orifice at the onset of systole is dependent on the leaflets as well as the subvalvular apparatus The cross sectional area of the leaflets is 1 5 to 2 2 times greater than the area of the orifice [6] Therefore when in the closed position the leaflets normally must fold as an accordion During systole one abnormal leaflet with ruptured or elongated chordae may bulge into the left atrium If not progressive then prolapse would occur without auscultatory phenomena Progressive prolapse would pull the abnormal leaflet away from the line of closure The other leaflet having lost the support of the abnormal leaflet would then spring centrally generating a high pitched click when its fibers become taut If this stretched leaflet is able to fill the orifice there will be no regurgitation and no systolic murmur If on the other hand the cusps remain widely separated both reflux of blood and a murmur will result This hypothesis would explain only those sounds which follow the onset of prolapse and not those appearing before the prolapse is evident In these latter cases, technical factors perhaps preclude optimal recording of the prolapse As in the patient presented in Fig 5 a different transducer orientation might reveal an earlier appearing prolapse

As previously demonstrated by Piemme and colleagues [47] intracardiac sounds are caused by abrupt acceleration and deceleration of the contents of fluid filled chambers with subsequent oscillation of the heart mass production of pressure transients and generation of sounds Thus the valve leaflet itself would not be expected to generate the systolic click That the leaflet is central to the production of this click however is supported by in vitro experiments with normal human mitral valves where lateral tension on the leaflets has been noted to produce high pitched sounds [44]

Angiographic evaluation has estimated the incidence of ballooning mitral valve to be 6 per cent [48] whereas the experience of the noninvasive laboratory at Montefiore Hospital suggests a frequency of at least 10 per cent Undoubtedly examination of more asymptomatic subjects accounts for the higher figure Echocardiography is a simple noninvasive technique which can be used to diagnose mitral valve prolapse regardless of the clinical presentation More specific than phonocardiography echocardiography may be used to diagnose ballooning of both as well as single mitral leaflets

Summary

Ten per cent of all patients referred to the echocardiography laboratory for diagnostic evaluation had mitral valve prolapse Of these 35 patients 19 (54 per cent) had prolapse of both the anterior and posterior mitral leaflets Of the 19 patients 13 had Type A or midsystolic prolapse whereas six had Type B or pansystolic prolapse of the mitral leaflets Simultaneous phonocardiographic examination of the patients revealed either midsystolic click and late systolic murmur pansystolic murmur or isolated click and short systolic murmur There was no apparent correlation between the echocardiographic prolapse pattern and the auscultatory events One patient

with Type A prolapse had no auscultatory abnormalities at the time of the examination It is suggested that the abnormal sounds may be generated by a redundant mitral leaflet rather than chordae tendineae

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Influence of pacemaker-induced tachycardia with A-V block on left ventricular blood velocity in man

Alberto Benchimol, M D
Kenneth B Desser, M D
Ting Fu Wang M D
Kiyoshi Mori M D
Phoenix Ariz

Recent study[1] has indicated the feasibility of directly measuring phasic, instantaneous and continuous blood velocities within the left ventricle of man Furthermore, the influence of atrial pacing on left ventricular blood velocity at 1 1 atrioventricular (A V) conduction has been described [2] During this latter investigation, it was noted that certain irregularities of peak flow velocity occurred when A V block ensued We report here the measurement of left ventricular blood velocity during atrial pacing and induced A V block

Material and method

Twenty eight subjects comprised the study group There were 21 men and seven women whose ages ranged from 28 to 73, with a mean of 54 years Eighteen patients had coronary artery disease, six had normal cardiovascular function and four had valvular heart disease Normal subjects were studied because of the presence of atypical chest pain or systolic murmurs originally considered to represent heart disease All diagnoses were made on the basis of complete right and left heart catheterization selective coronary cineangiography and indicator dilution curves

Left ventricular blood velocities were measured by radiotelemetry, using a method which has recently been described [1] Under local anesthesia (1 per cent lidocaine) a Doppler flowmeter catheter was introduced into the right or left brachial artery and advanced across the aortic valve into the left ventricle, where measurements were obtained A No 6 or 7 Zucker bipolar pacing catheter attached to the output of a Cordis or Medtronic pacemaker was introduced into a medial antecubital vein and advanced to the right atrium for the purpose of elective right atrial stimulation and pressure measurement Right atrial pressures were obtained by connecting the pacing catheter to a Statham P23Db strain gauge The right atrium was driven until either second degree A V block occurred or a pacing rate of 160 per minute was achieved with 1 1 A V conduction Second degree A V block ensued in 26 of 28 patients

Left ventricular blood velocities Lead II of the ECG at times tricuspid area phonocardiograms right atrial pressures and external carotid pulse tracings were simultaneously recorded in an Electronics for Medicine DR 12 oscilloscopic photographic recorder Flowmeter catheter tip stability and location were carefully monitored by fluoroscopic image intensification Blood velocities described in this report were measured at the left ventricular outflow tract or midcavity sites Outflow tract blood velocity is characterized by a large systolic ejection (S) wave followed by inconstant smaller diastolic (D) and presystolic (A) deflections Midcavity recordings under basal conditions are usually triphasic in character, with respective diastolic (D) presystolic (A), and systolic (S) wave forms of nearly equal amplitude [1]

From The Institute for Cardiovascular Diseases Good Samaritan Hospital Phoenix Ariz

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Reprint requests Alberto Benchimol M D Good Samaritan Hospital P O Box 2989 Phoenix Ariz 85062

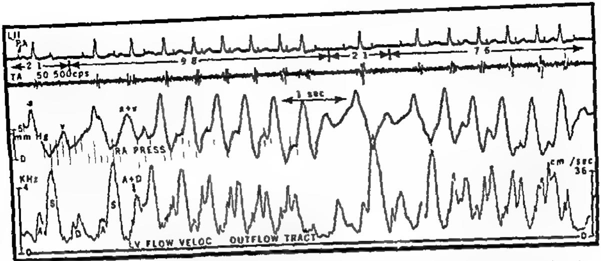

Fig 1 Simultaneously recorded Lead II (*LII*) of the ECG tricuspid area (*TA*) phonocardiogram right atrial (*RA*) pressure and left ventricular outflow tract blood velocity in a 49 year-old man with coronary artery disease Right atrial pacing (*PA* = pacing stimulus artifact) at a rate of 120 per minute produces A V block The respective A V conduction ratios are indicated Note the stepwise reduction of peak blood velocity during a period of 9 8 Type I Wenckebach A V block Prolonged P R intervals result in large presystolic blood velocities as "A" and "D" waves occur in combination (*A + D*) (*S* = systolic blood velocity wave)

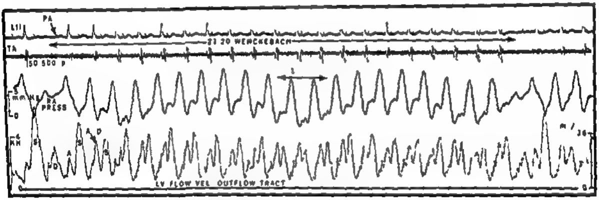

Fig 2 Recordings obtained from the same patient described in Fig 1 Here a 21 20 period of Wenckebach A V block produces minimal variation of peak outflow tract blood velocity Note the 40 per cent increase in blood velocity following the blocked atrial depolarization

Results

Left ventricular outflow tract blood velocity Outflow tract blood velocity was recorded during A V block in all 28 patients Type I A V Wenckebach block conduction ratios of 9 8 or less generally effected a stepwise reduction of peak left ventricular blood velocity as R R intervals on the ECG shortened Progressive P R prolongation during such Wenckebach periods produced large presystolic blood velocity waves in combination with encroachment of right atrial "v" waves by "a" waves (Fig 1) Longer Wenckebach periods with low conduction ratios produced minimal or no variation in peak left ventricular blood velocity during 1 1 A V conduction (Fig 2) There was usually a major augmentation of peak blood velocity following longer R R intervals produced as a consequence of the dropped beat In three subjects however bigeminal periods of 3 2 A V block resulted in larger peak left ventricular blood velocities when compared with 2 1 A V block despite identical R R intervals following the blocked atrial depolarization In all such cases, the second QRS complex during 3 2 A V block produced minimal or no phasic systolic blood velocity (Fig 3) A 55 year old woman without evidence of heart disease manifested an unusual ECG configuration of first degree A V

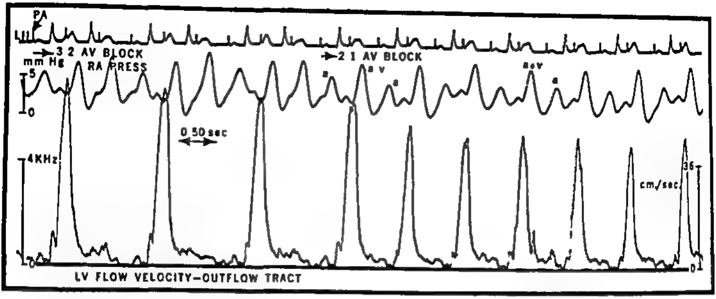

Fig 3 Simultaneously recorded Lead II (*LII*) of the ECG right atrial (*RA*) pressure and phasic left ventricular outflow tract blood velocity in a 42 year old man with coronary artery disease Right atrial pacing (*PA* = pacing stimulus artifact) at a rate of 130 per minute produces 3 2 and 2 1 A V block The second QRS complex of each 3 2 Wenckebach period generates little or no phasic systolic blood velocity Note that the first QRS complex of each 3 2 period produces a 20 to 30 per cent higher peak left ventricular blood velocity when compared with 2 1 block despite identical preceding R R intervals

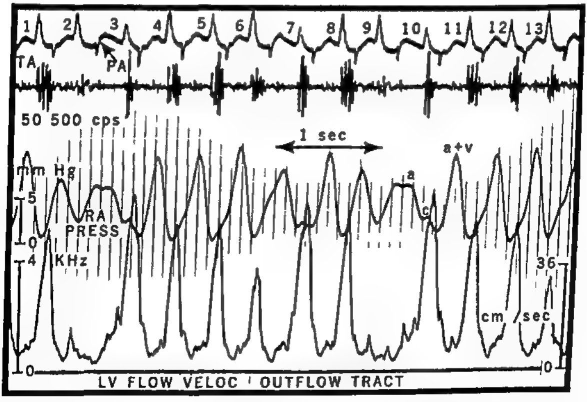

Fig 4 Simultaneous Lead II (*LII*) of the ECG tricuspid area (*TA*) phonocardiogram right atrial (*RA*) pressure and phasic left ventricular outflow tract blood velocity in a normal 55 year old woman Right atrial pacing (*PA* = pacing stimulus artifact) at a rate of 140 per minute results in 1 1 A V conduction and first degree A V block Unexpected abrupt prolongation of the P R interval occurs prior to QRS complexes Nos 3 7 and 10 which are different in their configuration Peak blood velocities increase and decrease in a cyclic fashion dependent on sudden lengthening of R R intervals QRS complexes Nos 2 6 and 9 which terminate each group of regularly conducted beats generate small (No 6) or negligable (Nos 2 and 9) phasic left ventricular systolic blood velocities

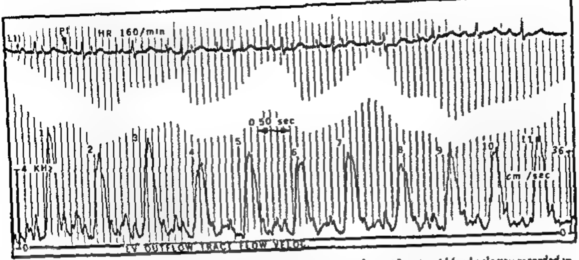

Fig 5 Simultaneous Lead II (*LII*) of the ECG and phasic left ventricular outflow tract blood velocity recorded in a *44* year old man with coronary artery disease Right atrial pacing (*PI* = pacing impulse) at a rate of 160 per minute effects 2 1 A V block and alternation of peak blood velocities Odd numbered blood velocities are greater than even numbered blood velocities in an alternating fashion Pacing was terminated after beat No 9

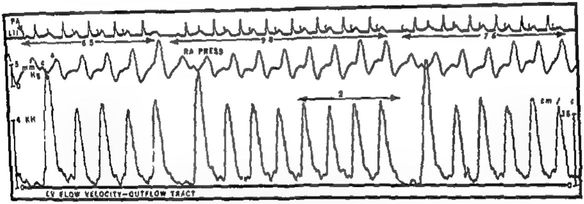

Fig 6 Simultaneously recorded Lead II (*LII*) of the ECG right atrial (*RA*) pressure and phasic left ventricular outflow tract blood velocity in a 4? year-old man with coronary artery disease Right atrial pacing (*PA* = pacing stimulus artifact) at a rate of 110 per minute produces Type I A V block in ratios of 6 5 9 8 and 7 6 The first QRS complex of each Wenckebach period results in the highest peak blood velocity subsequent blood velocities demonstrate alternation.

block during the course of right atrial pacing In this latter subject every third fourth or fifth atrial depolarization was associated with an unexpectedly prolonged P R interval and subsequent lower QRS complex amplitude on the ECG at 1 1 A V conduction This phenomenon effectively increased R R intervals and peak phasic left ventricular blood velocities increased and decreased in a cyclic fashion dependent on these changing diastolic pauses (Fig 4)

Blood flow velocity alternation Phasic left ventricular outflow tract blood velocity alternans was observed in three patients with A V block In a single subject peak flow velocity alternated during 2 1 A V block (Fig 5) Two other patients manifested left ventricular blood velocity alternation during Type I A V *Wenckebach* block Long pauses following blocked supraventricular impulses evoked the highest peak blood velocity followed by lower but alternating wave forms (Fig 6) Recordings in a *56 year old* man demonstrated atypical Wenckebach periods characterized by both progressively longer P R and R R intervals during right atrial pacing along with left

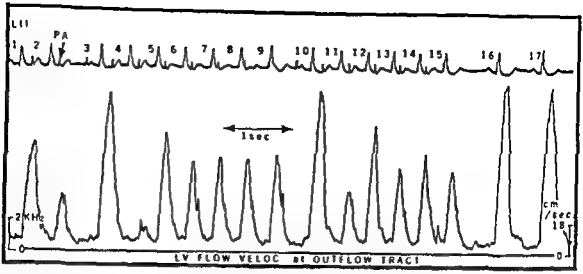

Fig 7 Lead II (*LII*) of the ECG and phasic left ventricular outflow tract blood velocity in a 56-year old man with coronary artery disease Right atrial pacing (*PA* = pacing stimulus artifact) at a rate of 140 per minute results in atypical 8 7 (beats Nos 3 to 9) and 7 6 (beats Nos 10 to 15) A V Wenckebach periods Note the P R and R R prolongation during 8 7 A V block QRS complexes Nos 4 and 11 represent the second beat of each period and are associated with the lowest peak velocities Note the blood velocity alternans during each Wenckebach period Pacing was terminated after QRS complex No 15

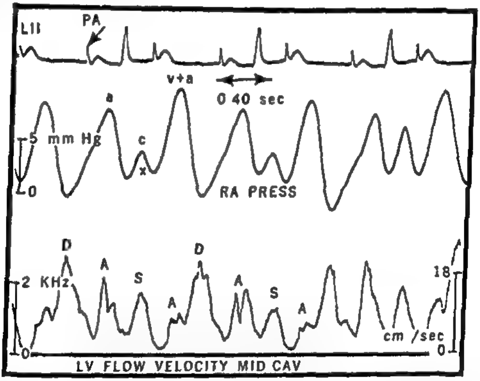

Fig 8 Simultaneously recorded Lead II (*LII*) of the ECG right atrial (*RA*) pressure and left ventricular midcavity blood velocity in a normal 56 year old man Right atrial pacing (*PA* = pacemaker stimulus artifact) at a rate of 120 per minute produces 2 1 A V block and a quadriphasic blood velocity pattern Large diastolic (*D*) waves are usually succeeded by progressively lower peak velocities produced by left atrial contraction (*A*) of the conducted beat the systolic (*S*) ejection wave and the blocked atrial depolarization (*A*) Note that peak phasic diastolic blood velocity is inscribed in conjunction with a Y trough of the right atrial pressure curve

ventricular blood velocity alternans Here, the second QRS complex of each Type I Wenckebach period was always associated with the smallest peak blood velocity (Fig 7)

Left ventricular midcavity blood flow velocity Midcavity blood velocities were measured in nine subjects during pacemaker induced tachycardia with A V block 2 1 A V block (four cases) produced characteristic quadriphasic midcavity blood velocity wave forms comprised of progressively declining amplitude, with each group of deflections initiated by the highest diastolic

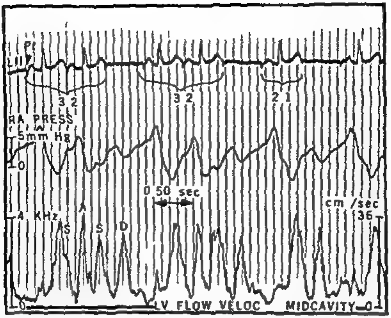

Fig 9 Simultaneously recorded Lead II (*LII*) of the ECG right atrial (*RA*) pressure and left ventricular midcavity blood flow velocity in a normal 28 year-old man Right atrial pacing (*PI* = pacer impulse) at a rate of 170 per minute results in 3 2 and 2 1 A V block The last atrial pacing impulse of each sequence of A V block results in no discernible P wave and absence of a terminal A wave on the blood velocity recording All recorded P waves QRS complexes and diastolic intervals are associated with "A" "S" and "D" waves, respectively

deflection (Fig 8) Type I Wenckebach A V block in five subjects effected changes in midcavity left ventricular blood velocity which reflected the varying P R and R R intervals In one such patient the last pacing stimulus for each sequence of A V block did not result in either atrial depolarization on the ECG or a waves on the blood velocity recording (Fig 9)

Discussion

This report represents the first description of phasic continuous left ventricular blood velocity during right atrial pacing and A V block in conscious man It was recently demonstrated that peak left ventricular blood velocity along with the amplitude of deflection on a simultaneously recorded external carotid pulse tracing diminish in direct relation to cardiac cycle length during right atrial pacing at 1 1 A V conduction [2] This diminution of peak flow velocity uniformly occurred at driving rates exceeding 120 per minute and was ascribed to less forceful left ventricular contraction reduced diastolic filling periods and smaller stroke output during the course of cardioacceleration In general the alterations of peak left ventricular blood velocity described here occurring during A V block are governed by the same factors described above including less effective atrial contraction to left ventricular blood velocities at extremely long P R intervals [2]

Blood velocity variation during 1 1 A V conduction In a single subject (Fig 4) unusual and striking variations of peak left ventricular blood velocity occurred despite right atrial stimulation at 1 1 A V conduction with first degree A V block. Here the flow velocity configurations resembled those noted during Type I A V block. Those P waves followed by the longest P R intervals effectively resulted in longer diastolic filling and more forceful left ventricular contractions in association with the lower amplitude and presumably aberrant QRS complexes Subsequent abbreviation of the R R interval produced less forceful left ventricular contractions smaller peak blood velocities and on occasion complete absence of phasic systolic flow Such beat to beat cycle length dependent alterations of blood velocity have been previously noted in man during other arrhythmias [3, 4]

Discrepancies in measured peak left ventricular blood velocity at identical preceding cycle lengths Interestingly bigeminal periods of 3 2 Wenckebach A V block in three patients

produced higher peak blood velocities than 2:1 A-V block even though the cycle lengths succeeding each blocked atrial depolarization were identical (Fig 3). In such cases the second QRS complex of each 3:2 period presumably did not generate enough left ventricular pressure to open the aortic valve and effect forward blood velocity. From the physiologic standpoint, such beats acted much the same as those produced during elective paired pacing. Ventricular depolarizations resulting in ineffective left ventricular contractions produced a functional prolongation of the R-R interval, thereby producing greater end-diastolic volumes and enhanced myocardial contractility.[1]

Blood velocity alternation during A-V block: Pulsus alternans associated with A-V block is an extremely unusual finding. Under most conditions the diagnosis of true alternation requires identification of more or less regular cycle lengths in order to rule out the influence of changing diastolic filling periods on the subsequent ventricular contraction. In the case of 2:1 A-V block (Fig 5) these criteria were satisfied, since the R-R intervals remained regular at the same time that left ventricular blood velocity alternans was observed. Alternating peak left ventricular blood velocities during A-V Wenckebach periods in two patients were particularly noteworthy (Figs 6 and 7). Under the latter conditions lower amplitude blood velocity waves did not occur as a consequence of long-short cycle length sequences and can be ascribed only to either alternating end-diastolic fiber lengths or contractile force during this arrhythmia.[8,9] On the other hand, changing P-R intervals, R-R intervals and stroke output, occurring during the course of Type I block, also influenced phasic left ventricular blood velocity. In 1971,[3] cyclic variations of aortic flow velocity were noted in 15 subjects during right atrial pacing and Type I A-V block. In three such patients, it was noted that the second beat and all even-numbered beats of Wenckebach periods produced diminished blood velocities, compatible with low flow beats during pulsus alternans. Successive odd-numbered beats of the periods resulted in higher but cyclically diminished flow velocity dependent on preceding cycle length. The data presented here provide the underlying alterations of left ventricular blood cell velocity responsible for the previously described aortic flow velocity changes. Although blood velocity alternation in combination with A-V Wenckebach block represents a complex hemodynamic state, it is apparent that in a total of five reported cases, the first QRS complex and all subsequent odd-numbered beats of the periods result in the more forceful left ventricular contractions. This finding can be ascribed to the longer diastolic cycle length which results in greater ventricular filling after the blocked P wave of the previous period, thereby initiating alternation. It is possible that even-numbered beats of a Wenckebach period may be associated with higher peak blood velocities during blood velocity alternation, but we have not observed this phenomenon.

Advantages and limitations of the technique: The Doppler flowmeter catheter utilized in this study measured the velocity of left ventricular blood cells flowing past its tip, and not volumetric flow.[1] Despite this limitation, there is no other currently employed method which can directly measure phasic, instantaneous characteristics of blood flow within the left ventricle of conscious intact man over prolonged periods and during sustained cardiac arrhythmias. Such study provides further insight into basic left ventricular abnormalities responsible for changes in blood velocity during A-V block.

Summary

Phasic instantaneous left ventricular blood velocity was measured by radiotelemetry in 28 subjects with a Doppler ultrasonic flowmeter catheter during atrial pacing and induced A-V block. Type I Wenckebach A-V block with conduction ratios of 9:8 or lower generally produced a stepwise reduction of peak left ventricular blood velocity in relation to shortened R-R intervals. Longer Wenckebach periods resulted in little or no blood velocity alteration during 1:1 A-V conduction. Those beats following a blocked atrial depolarization were associated with augmented blood velocities. In three subjects, bigeminal periods of 3:2 A-V block resulted in larger peak left ventricular blood velocities when compared with 2:1 A-V block despite identical R-R intervals following the blocked P wave. This latter phenomenon was attributed to diastolic augmentation of left ventricular contraction following the second and hemodynamically ineffective beat during 3:2 A-V block. Three patients manifested true blood

velocity alternation during second-degree A V block and changing R R intervals The variations in peak left ventricular blood velocity observed during atrial pacing and A V block are related to changing inotropic state and cycle length dependent alterations of left ventricular diastolic filling

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Follow-up catheterization of patients with myocardial infarction during coronary artery bypass surgery

C Thomas Fruehan, M D
Lewis W Johnson, M D
James L Potts, M D
Harold Smulyan M D
Frederick B Parker Jr M D
Robert H Eich, M D
Syracuse N Y

Coronary bypass surgery has become an accepted and common surgical procedure To assess properly the benefits and role of aortocoronary bypass surgery its risks and problems should be better understood One of these problem areas is the development of intraoperative myocardial infarction which has been reported to occur with an incidence as high as 29 per cent [1]

The purpose of this report is to review a series of patients with electrocardiographic evidence of intraoperative myocardial infarction which occurred during aortocoronary bypass surgery and to review the results of postoperative coronary arteriography and left ventriculography of these patients

Materials and methods

During a 30 month period, from October 1971, through April, 1974 239 patients had aortocoronary bypass surgery at State University Hospital Upstate Medical Center Syracuse N Y Excluded from the study group were 42 patients who had other concomitant cardiac surgical procedures such as resection of ventricular aneurysm, valvular surgery, ventricular septal defect closure, or internal mammary implantations The remaining 197 patients in the study group had aortocoronary bypass grafts only All patients were evaluated preoperatively by left heart catheterization left ventriculography and selective coronary cineangiography by the Sones and Shirey or Judkins[3] technique

All of the aortocoronary bypass operations were performed by the same team of surgeons All procedures were carried out under cardiopulmonary bypass with modified hypothermia at 32° C and with controlled ventricular fibrillation Grafts placed to the left coronary system were performed with intermittent aortic occlusion for brief periods not exceeding 10 minutes Right coronary grafts were performed by localized occlusion of the right coronary artery at the area of anastomosis

An electrocardiogram (ECG) was obtained on all patients within 48 hours before surgery Serial postoperative ECGs of all patients undergoing aortocoronary bypass were reviewed independently by three cardiologists Patients were considered to have had myocardial infarction only with unanimous opinion of the reviewers The diagnosis of myocardial infarction was made only in the presence of (1) characteristic change in QRS complexes from the preoperative ECG and (2) evolutionary changes in the ST T deflections in the same leads as the changed QRS

From the Departments of Medicine and Surgery State University of New York Upstate Medical Center Syracuse N Y

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Reprint requests C Thomas Fruehan M D State University Hospital of the Upstate Medical Center College of Medicine Department of Medicine Cardiology Section 750 E Adams St Syracuse N Y 13210

complexes ST T abnormalities alone were considered nondiagnostic

The characteristic change of the QRS complexes was nearly always the appearance of new Q waves essentially the classes I 1 and I 2 of the Minnesota Code of Blackburn and associates There was one exception to this requirement for new Q waves True posterior wall infarction was diagnosed when all the following findings were present in ECG leads $V_{1,2}$ (1) R/S ratio over 1 0 for the first time in the postoperative ECG s (2) increase in R/S ratio of over 100 per cent (3) appropriate ST T evolution and (4) absence of an intraventricular conduction defect

Serum enzymes (creatinine phosphokinase serum glutamic oxalacetic transaminase lactic dehydrogenase [CPK SGOT LDH]) were obtained preoperatively and on the first second and third postoperative days Upper limits of normal in our laboratory are CPK 139 units SGOT 40 units and LDH 207 units

Serum enzyme levels suggesting myocardial infarction after single vessel surgery were selected as CPK more than four times normal (> 556 units) SGOT more than twice normal (> 80 units) and LDH more than 360 units For multiple graft surgery these levels were CPK more than 9 times normal (> 1 251 units) SGOT more than 3 5 times normal (> 140 units) and LDH more than 560 units These levels are similar to the ninetieth percentile levels described by Alderman and co workers as correlating with myocardial infarction following coronary artery surgery

We have been able to obtain follow up catheterization studies on 11 survivors of intraoperative myocardial infarction Restudies have included standard left heart catheterizations with left ventriculography in both right and left anterior oblique projections selective coronary cineangiography and selective injection of the bypass graft(s)

Results

Intraoperative myocardial infarction was diagnosed by serial postoperative ECG s in 38 (19 per cent) of the 197 patients undergoing aortocoronary bypass procedures Eighty one per cent of patients diagnosed as having had myocardial infarction by ECG also had an elevation of at least one serum enzyme level (CPK SGOT LDH) sufficient to suggest myocardial infarction

Table I Wall involvement of intraoperative myocardial infarctions

Location	*No of patients*
Inferior	22
Anterior	6
True posterior	3
Anterior lateral	1
Anterior inferior	1
Inferior lateral	1
Inferior true posterior	2
Anterior lateral inferior	2
Total	38

Thirty-one of the 38 (82 per cent) infarctions involved a single wall the other seven (18 per cent) involved multiple walls (Table I) Twenty two of the intraoperative infarcts were of the inferior wall and another six involved the inferior wall and another wall Anterior lateral and true posterior wall infarctions were less frequent

Patients having multiple grafts were more likely to have intraoperative myocardial infarction Of the 197 patients of the study group 30 (15 per cent) had three or more grafts and 13 (43 per cent) of these 30 patients had intraoperative infarction In contrast 104 (53 per cent) patients had a single graft there were only eight (7 per cent) intraoperative infarctions in this group

Correlation of infarct location with graft site Thirty four of the 38 intraoperative infarctions occurred in a cardiac location supplied by the grafted coronary artery (Table II) For example four of five infarctions occurring in patients receiving only right coronary artery grafts involved the inferior wall Four of the intraoperative infarcts occurred in walls not perfused by the coronary artery which was grafted All four of these patients had occlusive disease not suitable for bypass in the arterial supply of the wall which infarcted

It is notable that most of the infarctions involved the inferior or true posterior wall even when multiple vessels were grafted In patients receiving grafts to all three major coronary arteries there were 10 infarctions eight occurred in the inferior wall alone one was posterior and one was inferior and lateral

Table II Correlation of infarct location with graft site

Coronary artery grafted	*Infarct location*	*No of infarcts*
LAD + LCA + RCA*	INF	8
	POST	1
	INF LAT	1
		10
LAD + RCA	INF	9
	INF POST	2
	ANT INF	2
	ANT	1
		14
LAD + LCA	INF	2†
	ANT	1
	ANT LAT	1
	ANT LAT INF	1
		5
RCA + LCA	INF	1
	POST	1
		2
LAD	ANT LAT INF	1
	POST	1†
		2
RCA	INF	4
	ANT	1†
		5
Total		38

LAD left anterior descending coronary artery LCA left circumflex coronary artery RCA right coronary artery ANT anterior wall INF inferior wall LAT lateral wall POST true posterior wall
†Infarction in wall not supplied by grafted coronary

Hospital course following intraoperative infarction The majority of patients with intraoperative myocardial infarction had a postoperative course not appreciably different from that of bypass patients without infarction however six of the 38 patients with intraoperative infarction developed severe and prolonged left ventricular failure Two of these patients died, another four who developed cardiogenic shock required intraaortic balloon counter pulsation, and survived

Follow up catheterization studies Eleven of the patients who survived intraoperative myocardial infarction have been recatheterized The average time between surgery and recatheterization was 10 months (range 2 weeks to 22 months)

Seven of the 11 patients had all grafts patent. Of these seven three had a new area of hypokinesis in the area of infarction the other four had ventriculograms which were normal or unchanged from the preoperative ventriculogram

Four of the 11 patients had at least one occluded graft three of these four had a new area of hypokinesis corresponding to the myocardial infarct Two of these three new hypokinetic areas were supplied by an occluded graft the third was supplied by a patent graft The fourth patient with a closed graft had a normal ventriculogram In all cases the area of hypokinesis when present corresponded to the ECG location of the intraoperative infarction

The graft patency rate of patients recatheterized after intraoperative infarction was 68 per cent (15 of 22) If the two patients who died (with all grafts occluded) are included the graft patency rate of these 13 patients is 54 per cent (15 of 28) This is in contrast to the 83 per cent graft patency rate of all patients restudied an average of 1 year after aortocoronary bypass surgery at this institution This difference is statistically significant ($p < 0.01$)

Discussion

The incidence of intraoperative myocardial infarction in this series is similar to that of previous reports The high incidence of inferior wall involvement of such infarctions has not been described previously

ECG diagnosis of myocardial infarction in patients undergoing cardiac surgery has been demonstrated to err on the side of underdiagnosis Brewer and associates[8] reported no false positive ECG diagnoses in a series of patients who had both ECG evidence of intraoperative myocardial infarction and autopsy confirmation Several patients in that report with autopsy evidence of myocardial infarction did not show diagnostic ECG evidence of infarction

The apparent discrepancy between patients showing ECG evidence of myocardial infarction without a diagnostic level of serum enzymes has been previously discussed by Alderman and associates[3] who has pointed out that the use of ninetieth percentile enzyme levels yielded a substantial number of false negative and false positive results as compared with ECG diagnosis

Bonchek and associates[7] described a group of patients with occluded bypass grafts In their series of 205 patients 52 (25 per cent) patients had at least one graft which occluded between the time of surgery and recatheterization Eight of these 52 patients had intraoperative myocardial infarction 44 of the 52 (85 per cent) had one or more occluded grafts without evidence of infarction This indicates that graft occlusion can occur without necessarily causing clinically recognizable infarction

Van Heeckeren and Ankeney reported[8] on eight patients recatheterized after intraoperative infarction one of these patients had all grafts patent and seven had occlusion of one or more grafts. Those authors did not report on the ventriculograms of patients with intraoperative infarctions

Our data differ from van Heeckeren s in that we found a larger proportion of intraoperative infarctions in the presence of patent grafts to the areas involved The finding of hypokinesis in the infarcted wall which was not present in the preoperative ventriculogram supports the fact that myocardial infarction did indeed occur

The occurrence of myocardial infarction in areas with patent grafts does not support previously published opinion[7] that the major threat to patients having bypass grafts is residual coronary disease which is not bypassed in this series most of the infarcts occurred in areas supplied by vessels which *were* bypassed and with patent grafts

There are many etiologic factors pertinent to intraoperative infarction in coronary bypass surgery Early graft occlusion appeared to have been a factor in some of these patients as demonstrated by the follow up *cineangiograms* Prolonged cardiopulmonary bypass with less than optimal perfusion of ischemic areas unable to be revascularized appears to be a likely *factor in* those patients with infarction in areas not perfused by the bypass grafts There remains a group of patients with patent grafts and electrocardiographic evidence of infarction in the *area* perfused by the graft To date we have no satisfactory explanation for these infarctions

We have no good explanation for the *failure to* find hypokinesis in five of the eleven patients with presumed intraoperative *infarction* It is possible that the infarction was not large enough to affect gross patterns of ventricular contraction

We conclude that intraoperative myocardial infarction [redacted] a fairly common problem of aortocoronary bypass surgery often involves an area supplied by a grafted vessel and is not necessarily related to graft closure

Summary

Of 197 consecutive patients having aortocoronary bypass grafts over a 30 month period [redacted] (19 per cent) had ECG evidence of myocardial infarction The infarctions occurred more commonly in patients receiving multiple grafts The infarctions were usually in areas supplied by grafted vessels The infarctions occurred most often in the inferior wall even when multiple vessels were *grafted* Eleven patients with intraoperative infarction have had repeat postoperative coronary arteriograms Seven had all grafts patent three of these patients had hypokinesis *of the* infarcted wall Four of the 11 patients had one or more occluded grafts three of these patients had an area of hypokinesis We conclude *that intra*operative myocardial infarction is a common problem in aortocoronary bypass surgery and is not necessarily caused by graft occlusion

Addendum

During the twelve months following the study period of this report 87 aortocoronary bypass procedures were done at this institution with an intraoperative infarction rate of 4.5 per cent (four infarcts) No single factor has been identified as a *cause for* the lower incidence The improvement is likely due to a combination of shorter periods of aortic occlusion increased aortic perfusion pressure improved surgical exposure, use of combined grafts and increased surgical experience

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Table II Correlation of infarct location with graft site

Coronary artery grafted	Infarct location	No of infarcts
LAD + LCA + RCA	INF	8
	POST	1
	INF LAT	1
		10
LAD + RCA	INF	[illegible]
	INF POST	2
	ANT INF	2
	ANT	1
		14
LAD + LCA	INF	2†
	ANT	1
	ANT LAT	1
	ANT LAT INF	1
		5
RCA + LCA	INF	1
	POST	1
		2
LAD	ANT LAT INF	1
	POST	1†
		2
RCA	INF	4
	ANT	1†
		5
Total		38

LAD left anterior descending coronary artery LCA left circumflex coronary artery RCA right coronary artery ANT anterior wall INF inferior wall LAT lateral wall POST true posterior wall
†Infarction in wall not supplied by grafted coronary

Hospital course following intraoperative infarction The majority of patients with intraoperative myocardial infarction had a postoperative course not appreciably different from that of bypass patients without infarction, however, six of the 38 patients with intraoperative infarction developed severe and prolonged left ventricular failure Two of these patients died another four who developed cardiogenic shock required intra aortic balloon counter pulsation and survived

Follow up catheterization studies Eleven of the patients who survived intraoperative myocardial infarction have been recatheterized The average time between surgery and recatheterization was 10 months (range, 2 weeks to 22 months)

Seven of the 11 patients had all grafts patent Of these seven, three had a new area of hypokinesis in the area of infarction, the other four had ventriculograms which were normal or unchanged from the preoperative ventriculogram

Four of the 11 patients had at least one occluded graft, three of these four had a new area of hypokinesis corresponding to the myocardial infarct Two of these three new hypokinetic areas were supplied by an occluded graft the third was supplied by a patent graft The fourth patient with a closed graft had a normal ventriculogram In all cases the area of hypokinesis when present, corresponded to the ECG location of the intraoperative infarction

The graft patency rate of patients recatheterized after intraoperative infarction was 68 per cent (15 of 22) If the two patients who died (with all grafts occluded) are included the graft patency rate of these 13 patients is 54 per cent (15 of 28) This is in contrast to the 83 per cent graft patency rate of all patients restudied an average of 1 year after aortocoronary bypass surgery at this institution This difference is statistically significant ($p < 0.01$)

Discussion

The incidence of intraoperative myocardial infarction in this series is similar to that of previous reports[4-8] The high incidence of inferior wall involvement of such infarctions has not been described previously

ECG diagnosis of myocardial infarction in patients undergoing cardiac surgery has been demonstrated to err on the side of underdiagnosis Brewer and associates[8] reported no false positive ECG diagnoses in a series of patients who had both ECG evidence of intraoperative myocardial infarction and autopsy confirmation Several patients in that report with autopsy evidence of myocardial infarction did not show diagnostic ECG evidence of infarction

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Experimental and laboratory reports

The effects of lidocaine on the canine ECG and electrophysiologic properties of Purkinje fibers

Michael R. Rosen, M.D.
Charles Merker, M.D.
Charles E. Pippenger, Ph.D.
New York, N. Y.

Lidocaine is a drug of demonstrated efficacy in the treatment of cardiac arrhythmias. In human subjects following administration of 1 to 2 mg per kilogram intravenously, lidocaine shortens the ventricular effective refractory period[1] and either has no effect on intraventricular conduction (measured using His bundle recording techniques) or depresses it slightly.[2] Studies of the effects of lidocaine in therapeutic concentrations on intraventricular conduction in experimental animals have revealed a slight but consistent depressant effect.[3]

There have been a number of studies of the cellular electrophysiologic basis for the antiarrhythmic effects of lidocaine. Bigger and Mandel[4,5] and Davis and Temte[6] showed that lidocaine 1 to 5 μg per milliliter accelerates repolarization and decreases the slope of phase 4 depolarization of canine cardiac Purkinje fibers perfused with Tyrode's solution containing 2.7 or 3 mM potassium. The effective refractory period decreased although not to the same extent as action potential duration. Neither Bigger and Mandel[4,5] nor Davis and Temte[6] noted any depressant effect of lidocaine on action potential amplitude and maximum upstroke velocity of phase 0 depolarization ($\dot{V}_{max}$) below concentrations of 11 to 50 μg per milliliter. In addition, Bigger and Mandel reported that lidocaine 2.3 μg per milliliter increased peak $\dot{V}_{max}$, and membrane responsiveness.

More recently Singh and Vaughan Williams[7] reported the effects of lidocaine on rabbit atrial and ventricular muscle. In these studies, in which both the species and the tissues differed from those used by Bigger and Mandel[4,5] and Davis and Temte,[6] the authors explored interactions between lidocaine and the extracellular potassium concentration ($[K^+]_o$). They found that when the $[K^+]_o$ was 5.6 mM, lidocaine 11.2 μg per milliliter induced prominent decreases in action potential amplitude and $\dot{V}_{max}$, changes which did not occur when $[K^+]_o$ was 3.0 mM. They suggested that the effects of lidocaine on cellular electrophysiologic properties may be modified by $[K^+]_o$ but that it acts much like other local anesthetics,[7,8] that is, by decreasing an inward sodium current during phase 0 depolarization.[9,10] Still more recently Weld and Bigger[11] and Gettes and associates[12] reported that at concentrations of 5 to 10 μg per milliliter lidocaine decreases $\dot{V}_{max}$ and prolongs the time for reactivation of the inward sodium current.

In terms of these studies it is difficult to identify all the mechanisms whereby lidocaine in the clinically therapeutic plasma concentration range of 1 or 2 to 5 μg per milliliter[3] suppresses ventricular arrhythmias. The data of Singh and Vaughan Williams,[7] of Bigger and Mandel,[4,5] and of Davis and Temte[6] are to some extent contradictory. Taking into account the differences between these studies with regard to species, tissue, and $[K^+]_o$, there is still a question as to whether lidocaine in clinically relevant concentrations decreases action potential amplitude and $\dot{V}_{max}$ and slows conduction or whether these are toxic effects seen only with high lidocaine concen

From the College of Physicians and Surgeons, Columbia University, New York, N. Y.

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Reprint requests: Michael R. Rosen, M.D., Department of Pharmacology, Columbia University College of Physicians & Surgeons, 630 W. 168th St., New York, N. Y. 1003_.

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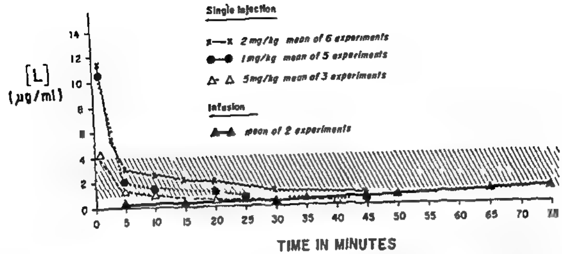

Fig 1 Plasma concentrations of lidocaine following single intravenous injections of 0.5, 1.0 and 2.0 mg per kilogram and intravenous infusions of 50 µg per kilogram per minute. The shaded area indicates the 1 to 4 µg per milliliter concentration range. Each curve is the average of all experiments done at a given lidocaine dosage schedule.

the stability of the method and the viability of the isolated tissues and the intact animal during blood perfusion.[17] The plasma potassium concentrations of the donor dogs in this series measured with an Orion potassium electrode and model 801 digital voltmeter were 3.9 to 4.8 mM per liter and varied less than 0.5 mM per liter during any one experiment. Donor and chamber blood pH, P_{O_2}, and P_{CO_2} were measured periodically during the studies with an IL 313 blood gas analyzer. These parameters were within the following ranges: pH, 7.35 to 7.4; P_{CO_2}, 32 to 45 mm; P_{O_2}, 89 to 95 mm. No significant differences between chamber and arterial levels were recorded. Donor ECG and arterial pressure were monitored continuously.[14]

The Purkinje fiber preparations were permitted to stabilize for one half hour during blood perfusion before the onset of a given experiment.[4] At this time we made control records of action potential amplitude, resting membrane potential, V_{max} of phase 0, action potential duration measured to 50 per cent (APD_{50}) and 100 per cent (APD_{100}) repolarization, membrane responsiveness, the effective refractory period, and conduction time. Lidocaine (Xylocaine 2 per cent, Astra Pharmaceutical) was administered in 14 experiments as a single intravenous injection of 0.5, 1.0, or 2.0 mg per kilogram and in six other experiments as an infusion of a 4, 10, 20, or 50 µg per kilogram per minute. Donor arterial blood (3 ml.) was drawn prior to and at frequent intervals during and after lidocaine administration to permit measurement of plasma lidocaine concentrations. In two experiments simultaneous samples were drawn from the donor femoral artery and from the chamber to determine the comparability of the donor plasma levels and the lidocaine levels in the bath. Differences were less than 0.3 µg per milliliter. Statistical analysis of data was performed by comparing control group values to group values after drug administration with Student's t test.[20]

Plasma lidocaine concentrations were determined by a modification of the method described by Keenaghan.[21] 1.0 ml. of plasma, 3.0 ml. of internal standard (prilocaine HCl, 1.0 µg per milliliter in distilled water), and 0.5 ml. of 5N sodium hydroxide were placed in a 15 ml. centrifuge tube. The sample was agitated briefly on a vortex mixer. 6.0 ml. of spectrograde methylene chloride were added, and the sample was shaken for 10 minutes on a platform shaker and centrifuged at 1,500 r.p.m. for 10 minutes. After centrifugation, the methylene chloride layer was transferred to another 15 ml. centrifuge tube and evaporated to dryness in a Buchler Rotary Evapo-Mix. For gas liquid chromatographic analysis 75 µl of chloroform were added to the dry residue and vortexed for 30 seconds, and 2 µl of the $CHCl_3$ were injected into the gas chromatographic column.

trations, the former effect would suggest that in the therapeutic concentration range lidocaine acts by a mechanism different from that of other local anesthetics, as has been suggested by Bigger and Mandel[4]

The purpose of the present investigation was to employ a recently developed blood perfusion technique[14] to study the effects of clinically relevant plasma lidocaine concentrations on the electrophysiologic properties of isolated canine Purkinje fibers The questions asked were (1) in the therapeutic plasma concentration range and at normal plasma $[K^+]_o$ does lidocaine have a "local anesthetic" effect on the action potential decreasing amplitude, V_{max}, and membrane responsiveness[9,10] and (2) when an arrhythmia is present and action potentials are 'depressed' (with decreased resting membrane potential, action potential amplitude, and V_{max}, whether due to disease digitalis toxicity or other interventions) does a concentration of lidocaine sufficient to suppress the arrhythmia increase or further decrease action potential amplitude, V_{max}, and conduction Through these observations we hoped to clarify to some extent the cellular electrophysiologic basis for the antiarrhythmic effects of lidocaine in patients

Methods

The method for blood perfusion has been applied previously to the study of procaine amide and ouabain[14,17] Use of this system permits single injections or infusions of a drug into the venous circulation of a donor dog and the perfusion of isolated cardiac Purkinje fiber bundles with donor arterial blood The effects of pharmacologic agents on the donor electrocardiogram (ECG) and on the electrophysiologic events occurring in the isolated tissues can then be observed and correlated with plasma drug concentrations[15]

Twenty two blood perfusion experiments were conducted In each a mongrel dog weighing 20 to 30 kilograms was anesthetized with sodium pentobarbital 30 mg per kilogram Its heart was rapidly removed through a right lateral thoracotomy and the Purkinje fiber bundles excised and pinned to the wax bottom of a Lucite perfusion chamber having a volume of 4 5 ml The chamber was perfused with Tyrode s solution[18] having a potassium concentration $[K^+]_o$ of 4 mM at a temperature of 36 to 37° C and a flow rate of 10 to 13 ml per minute The method for stimulating the preparation through Teflon coated silver wire bipolar electrodes and delivering both basic drive (S_1) and premature test (S_2) stimuli has been described previously[19]

Purkinje fibers were impaled with glass capillary microelectrodes with tip diameters less than 1 μ and resistances of 10 to 20 megohms The methods used to calibrate the equipment to record transmembrane action potentials and to measure V_{max} and membrane responsiveness (the relationship of V_{max} of phase 0 to the level of membrane potential at which an action potential is initiated) have been described previously[11,19] Measurements of action potential amplitude resting membrane potential, V_{max}, membrane responsiveness conduction time action potential duration, and the effective refractory period were performed on line by the methods of Gelband[20] and Myerburg[21] and their co workers

For studies of the effective refractory period two microelectrodes were impaled in the free running Purkinje fiber Premature depolarizations (R_2) were initiated after every seventh to eighth drive (R_1), and the earliest R_2 initiated at the proximal electrode site which propagated to the distal electrode site was considered to define the end of the effective refractory period

For studies of conduction the time for propagation of an action potential (R_1) between two intracellular microelectrodes impaled in an unbranched free running Purkinje fiber bundle was recorded at rapid oscilloscope sweep speeds The conduction time for premature depolarizations (R_2) was determined in studies of the effective refractory period and during the measurement of membrane responsiveness[11] To study automaticity the preparation was permitted to attain a stable spontaneous rate and rhythm during perfusion with Tyrode's solution Following the onset of blood perfusion, the spontaneous rate and rhythm were observed for another 30 minutes before drug was administered

To initiate blood perfusion a donor dog was anesthetized with sodium pentobarbital 30 mg per kilogram, and heparinized with sodium heparin 3 mg per kilogram A femoral artery and vein were cannulated and arterial blood was pumped into the tissue chamber in place of Tyrode s solution Effluent from the chamber was pumped through an air trap and infused into the femoral vein We have previously demonstrated

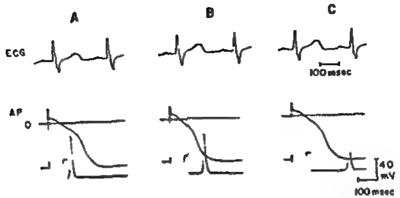

Fig 2 Effects of lidocaine on the donor ECG and a Purkinje fiber action potential. Stimulus cycle length 500 msec Plasma [K]$_o$ = 3 9 mM *Panel A* control. *ECG* P R 75 msec., QRS 43 msec., Q T 160 msec., R R 305 msec *AP* the upper trace in this panel and subsequent records is the action potential. The lower trace is a 200 V per second calibration followed by the electronically differentiated V_{max} of phase 0 *AP* amplitude 1 4 mV RMP −93 mV V_{max} 440 V per second APD$_{50}$ 1 0 msec., APD$_{90}$ 280 msec *Panel B* 5 minutes after a 1 mg per kilogram lidocaine injection plasma lidocaine concentration = 2 μg per milliliter *ECG* P R 5 msec., QRS 48 msec Q T 168 msec., R R 315 msec. *AP* amplitude 116 mV RMP −91 mV., V_{max} 405 V per second, APD$_{50}$ 130 msec., APD$_{90}$ 232 msec *Panel C* 30 minutes after lidocaine injection plasma concentration = 0 7 μg per milliliter *ECG* P R 5 msec., QRS 46 msec., Q T 170 msec R R 310 msec *AP* amplitude 122 mV., RMP −93 mV., V_{max} 435 V per second APD$_{50}$ 160 msec., APD$_{90}$ 265 msec

A Hewlett Packard Model 7610 gas chromatograph equipped with dual flame ionization detectors was used for all analyses Glass columns one quarter inch OD (2 mm ID) were packed with 3 per cent OV 210 on Gas Chrom Q 80/100 mesh and conditioned with a slow nitrogen flow (10 ml per minute) at 240 C for 24 hours prior to use Operating parameters were injector 250 C oven 200 C and detector 300 C Nitrogen was used as the carrier gas at a flow rate of 32 ml per minute Hydrogen and air were adjusted to give optimum detector response Lidocaine standard curves were prepared daily by adding appropriate concentrations of lidocaine HCl to pooled plasma and carrying the sample through the extraction procedure Quantitation was based on the peak height ratio of lidocaine to the internal standard Responses were linear over the range of 1 to 15 μg per milliliter and recoveries of added lidocaine ranged from [illegible] to 98 per cent

To study the effects of lidocaine on digitalis induced arrhythmias ouabain 60 μg per kilogram was given intravenously to the donor following stabilization of the blood perfused Purkinje fiber bundles We have previously demonstrated the comparability of isolated and donor Purkinje fiber uptake of ouabain and electrophysiologic changes induced by ouabain using this method The ECG and the Purkinje fiber action potentials were recorded before and after the onset of a toxic arrhythmia in the donor A single intravenous lidocaine injection of 1 or 2 mg per kilogram was then administered and the ensuing changes in the ECG and action potentials were recorded

In eight additional experiments Purkinje fiber bundles were excised from the heart pinned to the chamber and studied during perfusion with Tyrode's solution ([K] = 4 mM) Lidocaine dissolved in separate reservoirs of Tyrode's solution to make a final concentration of 2 μg per milliliter was then perfused and its effects on electrophysiologic properties were observed

Results

Studies of blood perfused Purkinje fibers Fig 1 shows the plasma concentration curves obtained following single intravenous injections of lidocaine 0 5 1 0 and 2 0 mg per kilogram and infusions of 50 μg per kilogram per minute The shaded area (lidocaine 1 to 4 μg per milliliter) approximates the usual therapeutic plasma concentration in man[11] and is the lower lidocaine concentration range in which measurable changes in action potential properties consistently occurred

Table I shows the effects on the donor animal ECG and arterial pressure of the lidocaine concentrations attained following single injections The only parameter to be altered consist

Table I Effects of single injections of lidocaine on donor ECG and arterial pressure*

Plasma [L] (µg/ml)	*0 min* *0* *Control*	*5 min* *4 1 9 9* *% of control*	*15 min* *1 0 4 0* *% of control*	*45 min.* *0.2 0 9* *% of control*
A FCG interval (msec)				
P R	84.5 ± 10 7 (16)	103 ± 9 (6)	99 ± 9 (16)	100 ± 5 (8)
QRS	48 5 ± 6 6 (16)	103 ± 10 (6)	102 ± 3 (16)	103 ± 5 (8)
Q T	181 6 ± 30 4 (16)	90 ± 7 (6)	97 ± 7 (16)	99 ± 5 (8)
R R	510 ± 66 (16)	106 ± 8 (6)	100 ± 12 (16)	101 ± 4 (8)
B Arterial pressure (mm Hg)				
Systolic	133 ± 16	100 ± 1	100 ± 1	99 ± [illegible]
Diastolic	87 ± 11 (16)	98 ± 3 (6)	101 ± 2 (16)	99 ± [illegible] (8)

Results expressed as mean ± S D Number of observations is in parentheses For each ECG recording the mean of 10 consecutive cycles was taken. Readings made following single lidocaine injections of 0 5 to 2 mg per kilogram

Table II Effects of lidocaine on the action potential, conduction time and effective refractory period

Plasma [L] (µg/ml)	*Control* *0 min* *0*	*5 min* *4 1 9 9*	*15 min* *1 0 4 0*	*45 min.* *0.2 0 9*
Effects of single injections of lidocaine on electrophysiologic properties of isolated Purkinje fibers				
AP amplitude (mV)	121 ± 3 4 (21)	112 7 ± 9 2§ (21)	117 1 ± 5 7§ (21)	119 1 ± 3 1 (21)
RMP (−mV)	87 6 ± 3 5 (16)	86 3 ± 5 3 (15)	87 1 ± 3 3 (15)	88 4 ± 1 9 (15)
V_m (V/sec)	481 ± 53 (21)	405 ± 43 (21)	471 ± 65 (21)	479 ± 60 (18)
APD $_{90}$ (msec)	30[illegible] ± 24 (21)	281 ± 19 (21)	272 ± 23§ (21)	299 ± 35 (21)
Conduction time†	100% (8)	111 ± 13% (8)	102 ± 12% (8)	98 ± 6% (8)
Effects of lidocaine on the ERP				
ERP [illegible] S_1 (msec)	235 ± 12 (6)		219 ± 7‖ (6)	234 ± 13 (4)
[illegible] R_1 (msec)	239 ± 13 (6)		229 ± 3 (6)	238 ± 12 (4)
Activation voltage (−mV)‡	60 1 ± 7 3 (6)		68 4 ± 8 1 (6)	61 5 ± 7 6 (4)

Results expressed as mean ± S D Number of observations in parentheses Cycle length 800 msec Readings taken after single lidocaine injections of 0 5 to 2 0 mg per kilogram

†For the purpose of this table the control conduction time in each experiment was recorded as 100 per cent and subsequent changes in conduction were tabulated as per cent changes from this value

‡Membrane potential at which the R indicating the end of the ERP was initiated

§P < 0 01 compared to control group

‖P < 0 02 compared to control group

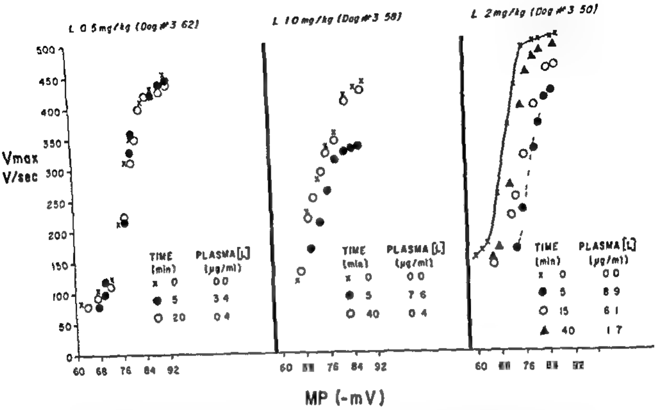

Fig 4 Effects of lidocaine on membrane responsiveness Three experiments Stimulus cycle length 800 msec Abscissa membrane potential ordinate V For each experiment the time of measurement of the responsiveness curve and the plasma lidocaine concentration at the time are listed Lidocaine 0 5 mg per kilogram had no effect on membrane responsiveness Lidocaine 1 0 mg per kilogram initially depressed membrane responsiveness and control values were subsequently attained Lidocaine 2 mg per kilogram resulted in higher initial plasma levels and a greater depression of responsiveness This was followed by a return toward control values.

trations of 1 to 4 µg per milliliter had no consistent effect on the conduction time for the R In some instances conduction time was unchanged in others it was slowed In no experiment was conduction time for an R accelerated In many instances however conduction time for an R_1 was accelerated The interactions between changes in the R R interval the activation voltage membrane responsiveness and conduction were further explored in Purkinje fiber bundles perfused with Tyrode s solution These results are presented in a subsequent section

In the studies of membrane responsiveness plasma lidocaine concentrations of 4 1 to 9 9 µg per milliliter consistently were associated with a depression of the membrane responsiveness curve Concentrations of 1 to 4 µg per milliliter were associated with either no change or a slight depression of the curve Fig 4 shows the effects of lidocaine on membrane responsiveness of three blood perfused Purkinje fibers When 0 5 mg per kilogram was injected into the donor animal no change in Purkinje fiber membrane responsiveness occurred When 1 0 mg per kilogram was given the curve was depressed at 5 minutes and returned to control at 40 minutes When 2 0 mg per kilogram were given the curve was even more markedly depressed initially and then returned toward control

The effects of lidocaine on the automaticity of spontaneously firing Purkinje fiber bundles were studied in eight experiments In all of these lidocaine 1 to 4 µg per milliliter, induced a decrease in the slope of phase 4 depolarization and a slowing of spontaneous rate Concentrations less than 1 µg per milliliter did not measurably alter automaticity or the slope of phase 4

Studies of digitalis toxicity The studies of digitalis toxicity were performed to permit the evaluation of lidocaine effects on depressed Purkinje fibers Fig 5 shows one of four experiments in which the donor animal was given

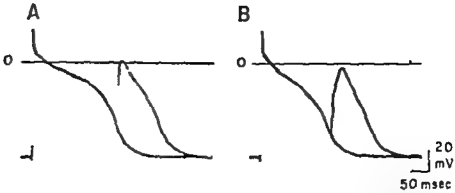

Fig 3 Effects of lidocaine on the Purkinje fiber effective refractory period Stimulus cycle length 800 msec In each panel the R and the R R_2 interval indicating the end of the effective refractory period are superimposed Plasma [K] = 4 2 mM *Panel A* control *AP* amplitude 122 mV RMP −89 mV APD_{50} 178 msec APD_{100} 316 msec R R_2 224 msec activation voltage R = −60 mV *Panel B* 20 minutes after a 2 0 mg per kilogram lidocaine injection plasma lidocaine concentration 2 2 μg per milliliter *AP* amplitude 120 mV RMP −89 mV APD 130 msec ADP_{100} 260 msec R R 195 msec activation voltage R = −66 mV

ently (but not significantly) was the ECG Q T interval which decreased in the 4 1 to 9 9 μg per milliliter range

Table II summarizes the effects of lidocaine administered as a single injection on the electro physiologic properties of the isolated Purkinje fiber bundles In the initial 5 minutes after injec tion when plasma concentrations were 4 1 to 9 9 μg per milliliter lidocaine induced decreases in action potential amplitude, V_m , and action potential duration, and a slowing of conduction of the R_1 At 15 minutes when lidocaine concentra tion was 1 to 4 μg per milliliter, action potential amplitude and duration still were decreased although less so than previously, while V_{max} had returned to near control values Conduction was either slightly depressed or normal At 45 minutes when lidocaine was 0 2 to 0 9 μg per milliliter control or near control values had been attained for all variables When lidocaine was administered as an infusion of 50 μg per kilogram per minute, attainment of plasma concentrations in the 1 to 4 μg per milliliter range was accom panied by changes in action potential characteris tics comparable to those shown for the same plasma levels in Table II

Fig 2 shows one experiment illustrating the effects of lidocaine on the ECG and action poten tial characteristics Panel *A* is a control panel *B* shows the changes recorded 5 minutes after a lidocaine injection of 1 mg per kilogram and at a plasma concentration of 2 μg per milliliter The changes include a decrease in AP amplitude and V_m and an acceleration of repolarization In panel *C* after 30 minutes the plasma lidocaine concentration was 0 7 μg per milliliter and control values for the action potential had again been attained No changes were seen on the ECG

The actions of lidocaine, 1 to 4 μg per milliliter on the effective refractory period are shown in the lower part of Table II In every instance, the duration of the effective refractory period de creased although to a lesser extent than the duration of the action potential As a result the effective refractory period was prolonged with respect to action potential duration In two ex periments in which lidocaine concentrations of 4 1 to 9 9 μg per milliliter were attained similar (although quantitatively greater) alterations in the effective refractory period occurred In all the studies of the effective refractory period, there was an increase in the activation voltage, that is the transmembrane potential at which the R_2 delineating the end of the effective refractory period was initiated *

Fig 3 shows the effects of an injection of lidocaine 2 mg per kilogram on the effective refractory period At a plasma concentration of 2 2 μg per milliliter (panel *B*) action potential amplitude was decreased and RMP was unchan ged The voltage time course of repolarization was accelerated resulting in a decrease in APD_{100} from 316 to 260 msec The duration of the effec tive refractory period decreased from 224 to 195 msec and the R_2 now arose at an activation voltage of −66 mV compared to a control of −60 mV Even though activation voltage was more negative the rate of rise of phase 0 of the R_2 was decreased

As previously mentioned, lidocaine in concen

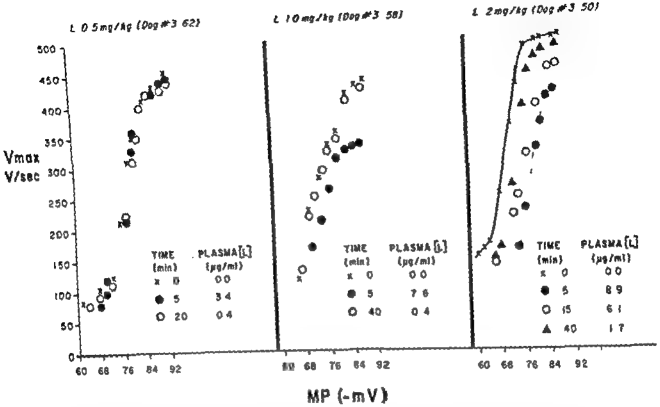

Fig 4 Effects of lidocaine on membrane responsiveness Three experiments Stimulus cycle length 800 msec Abscissa membrane potential, ordinate V_{max} For each experiment the time of measurement of the responsiveness curve and the plasma lidocaine concentration at the time are listed Lidocaine 0 5 mg per kilogram had no effect on membrane responsiveness Lidocaine 1 0 mg per kilogram initially depressed membrane responsiveness and control values were subsequently attained Lidocaine 2 mg per kilogram resulted in higher initial plasma levels and a greater depression of responsiveness This was followed by a return toward control values.

trations of 1 to 4 µg per milliliter had no consistent effect on the conduction time for the R In some instances conduction time was unchanged in others it was slowed In no experiment was conduction time for an R accelerated In many instances however conduction time for an R_2 was accelerated The interactions between changes in the III R interval the activation voltage membrane responsiveness and conduction were further explored in Purkinje fiber bundles perfused with Tyrode s solution These results are presented in a subsequent section

In the studies of membrane responsiveness plasma lidocaine concentrations of 4 1 to 9 9 µg per milliliter consistently were associated with a depression of the membrane responsiveness curve Concentrations of 1 to 4 µg per milliliter were associated with either no change or a slight depression of the curve Fig 4 shows the effects of lidocaine on membrane responsiveness of three blood perfused Purkinje fibers When 0 5 mg per kilogram was injected into the donor animal no change in Purkinje fiber membrane responsiveness occurred When 1 0 mg per kilogram was given the curve was depressed at 5 minutes and returned to control at 40 minutes When 2 0 mg per kilogram were given the curve was even more markedly depressed initially and then returned toward control

The effects of lidocaine on the automaticity of spontaneously firing Purkinje fiber bundles were studied in eight experiments In all of these lidocaine 1 to 4 µg per milliliter induced a decrease in the slope of phase 4 depolarization and a slowing of spontaneous rate Concentrations less than 1 µg per milliliter did not measurably alter automaticity or the slope of phase 4

Studies of digitalis toxicity The studies of digitalis toxicity were performed to permit the evaluation of lidocaine effects on depressed Purkinje fibers Fig 5 shows one of four experiments in which the donor animal was given

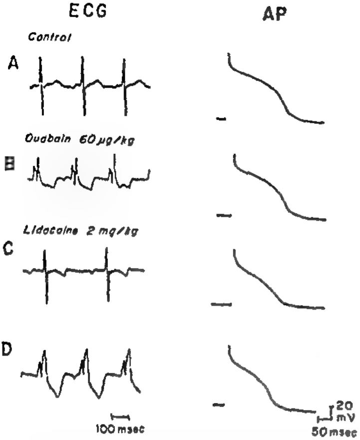

Fig 5 Effects of lidocaine injection following administration of a toxic dose of ouabain cycle length 600 msec Plasma [K] 4 6 mM *Panel A* control *ECG* normal sinus rhythm P R 85 msec QRS 45 msec Q T 205 msec R R 350 msec *AP* amplitude 116 mV APD 185 msec APD 300 msec *Panel B* 50 minutes following a 60 µg per kilogram ouabain injection *ECG* ventricular tachycardia *AP* amplitude 108 mV APD 160 msec APD 265 msec *Panel C* 2 minutes after a 2 mg per kilogram lidocaine injection plasma concentration 8 µg per milliliter *ECG* normal sinus rhythm P R 130 msec QRS 50 msec Q T 205 msec R R 520 msec *AP* amplitude 99 mV APD 95 msec APD 230 msec *Panel D* after 40 minutes plasma lidocaine concentration 1 1 µg per milliliter *ECG* ventricular tachycardia *AP* amplitude 106 mV APD 115 msec APD 240 msec

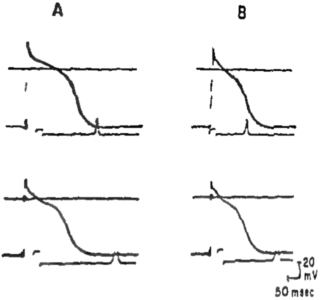

Fig 6 Effect of lidocaine 2 µg per milliliter in Tyrode s solution on Purkinje fiber action potentials Tyrode [K] = 4 mM stimulus cycle length 630 msec *A* two control action potentials Upper panel amplitude 126 mV RMP −86 mV $\dot{V}_{max}$ 600 V per second APD_{50} 175 msec APD_{90} 270 msec Lower panel amplitude 115 mV RMP −86 mV $\dot{V}_{max}$ 476 V per second APD_{50} 150 msec APD_{90} 270 msec *B* 20 minutes after onset of lidocaine perfusion Upper panel amplitude 1? mV RMP −86 mV $\dot{V}_{max}$ 540 V/sec APD_{50} 133 msec APD_{90} 250 msec Lower panel amplitude 112 mV RMP −86 mV $\dot{V}_{max}$ 400 V per second APD_{50} 135 msec APD_{90} 250 msec

ouabain 60 µg per kilogram Thirty minutes after ouabain injection ventricular premature depolarizations commenced, followed shortly thereafter by ventricular tachycardia Panel *B* was recorded 20 minutes after the onset of ventricular premature depolarizations At this time, both the ventricular tachycardia and the action potential (which showed a decrease in amplitude and an acceleration of repolarization) had been stable for 15 minutes A 2 0 mg per kilogram lidocaine injection (panel *C*) resulted in a rapid return to sinus rhythm associated with a further decrease in action potential amplitude and acceleration of repolarization As the plasma lidocaine concentration decreased (panel *D*), ventricular tachycardia recurred action potential amplitude increased and the voltage time course of repolarization was prolonged In all four experiments on ouabain toxicity lidocaine concentrations sufficient to suppress digitalis induced arrhythmias decreased action potential amplitude and V_m and accelerated repolarization

Studies of Purkinje fibers perfused with Tyrode s solution In five experiments Purkinje fiber bundles were perfused with Tyrode s solution containing lidocaine 2 µg per milliliter Records from one experiment are shown in Fig 6 Here 20 minutes of lidocaine perfusion resulted in decreases in action potential amplitude and V_m and an acceleration of repolarization In three of the five experiments conduction for the R_1 was unchanged In two it was slowed slightly As mentioned with regard to Figs 3 and 4 while conduction for the R_1 was unchanged or slowed by lidocaine that for an R_2 was often accelerated Because the effects on the action potential of lidocaine (2 µg per milliliter) dissolved in Tyrode s solution were similar to those of 1 to 4 µg per milliliter concentrations during blood perfusion we felt it was reasonable to use the Tyrode perfused fibers to explore the interrelationships

between R_1R_2 intervals activation voltages membrane responsiveness and conduction

Results of one of three such experiments are shown in Fig 7 The effects of lidocaine 2 µg per milliliter on Purkinje fiber repolarization (upper trace R R_2 interval) on conduction time for an R_2 or premature depolarization (*CT* middle trace) and on membrane responsiveness (lower trace) are displayed Lidocaine perfusion led to a decrease in APD_{100} from a control of 350 to 290 msec but did not alter resting membrane potential V_m for the fully repolarized fiber was 505 V per second during control and 475 V per second with lidocaine and conduction of an R_2 originating just after full repolarization was slowed by lidocaine from 3 8 to 4 2 msec (approximately 10 per cent) In addition lidocaine slowed conduction and decreased V_m for all levels of activation voltage studied

At very short R R intervals (either equal to or slightly longer than the R_1R_2 delineating the end of the effective refractory period) conduction for the R_2 was accelerated during lidocaine perfusion The explanation for this observation is shown in Fig 7 the values to be referred to all fall on the broken line superimposed on the figure During control at an R_1 R interval of 280 msec (the control effective refractory period) activation voltage was −64 mV V_m was 70 V per second and conduction time was 5 25 msec Lidocaine accelerated the voltage time course of repolarization to such an extent that the same R R_2 interval of 280 msec occurred just prior to full repolarization at an activation voltage of −88 mV V_m here was 475 V per second and conduction time 4 2 msec Hence if premature depolarizations (R_2) occur at short coupling intervals and the coupling intervals do not change during lidocaine perfusion marked increases in activation voltage and V_m and an acceleration of conduction occur concurrently with the lidocaine induced accelerated voltage time course of repolarization These occur despite the fact that V_m is decreased and conduction is slowed for any impulse arising at the same activation voltage both before and during lidocaine perfusion

Discussion

The purpose of these studies was to determine whether lidocaine at a clinically relevant plasma concentration has a local anesthetic effect on the action potential as suggested by Singh and Vaughan Williams[7,8] or whether it might increase V_m and membrane responsiveness and thereby improve conduction as suggested by Bigger and Mandel Our results indicate that lidocaine in plasma concentration of 1 to 4 µg per milliliter induces small but consistent decreases in action potential amplitude and V_m and decreases automaticity It accelerates the voltage time course of repolarization and decreases the effective refractory period although not to the same extent as action potential duration and increases the activation voltage at which the R_2 indicating the end of the effective refractory period arises In the 4 1 to 9 9 µg per milliliter plasma concentration range these changes are more marked and in addition there are consistent decreases in membrane responsiveness and in conduction velocity for R_2 At none of these lidocaine concentrations did we see changes in resting membrane potential or increases in V_m

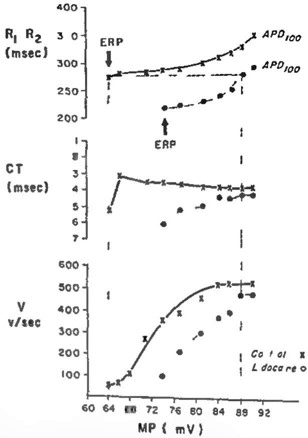

Fig 7 Factors modifying conduction of premature depolarizations Abscissa membrane potential lower ordinate V_m for R middle ordinate (CT) conduction time for R upper ordinate R_1R_2 interval. *ERP* indicates the effective refractory period. See text for discussion

or membrane responsiveness The observations made for normal Purkinje fibers also applied when effects of lidocaine on digitalis induced electrophysiologic changes were studied However with respect to the studies of digitalis toxicity, it should be noted that we were inducing toxicity in previously normal Purkinje fibers Hence the results noted may not be entirely applicable to clinical situations of digitalis toxicity where fibers are diseased prior to drug administration Our findings with regard to the effective refractory period are in agreement with those of the other groups who investigated lidocaine effects in Tyrode perfused tissues[1,4], our observations on action potential amplitude V_{max} and conduction support those of Singh and Vaughan Williams

To be sure the effects of lidocaine on action potential amplitude and V_{m} were small during maintenance of the 1 to 4 μg per milliliter concentration range and membrane responsiveness and conduction were depressed inconsistently However the 1 to 4 μg per milliliter range does not encompass all concentrations which are attained during the course of clinical therapy with lidocaine To illustrate administration of a single injection of lidocaine (Fig 1) results in transiently elevated plasma concentrations Despite the brevity of the period during which higher concentrations are maintained equilibration of lidocaine with Purkinje fibers is apparently rapid enough to permit a pronounced effect on action potentials to occur This is evident from Fig 4, where, following lidocaine injections of 1 to [illegible] mg per kilogram membrane responsiveness was depressed The depression of membrane responsiveness was greatest when plasma lidocaine concentrations were elevated to a level that would be considered toxic in a steady state However, this level is regularly but transiently attained in therapeutic situations and appears to exert a pronounced effect on action potential properties It is an effect akin to that described for procaine amide, and other local anesthetics[9, 10, 14, 15]

Although lidocaine depresses membrane responsiveness and slows conduction, this does not necessarily indicate that in all instances conduction velocity for a premature depolarization will be depressed Referring to Fig 7, it is apparent that for any $R_1 R_2$ interval, the acceleration of repolarization induced by lidocaine resulted in an increase in activation voltage In spite of the lidocaine induced decrease in membrane responsiveness the V_{max} of the R_2 occurring at approximately the control $R_1 R_2$ interval was increased

It is apparent from Fig 7 that the coupling intervals at which conduction would most likely improve are those which under control conditions are equal to or only slightly longer than the effective refractory period Premature depolarizations occurring at these relatively short intervals, which would be most likely to propagate decrementally and induce aberrant conduction show an improvement in conduction as a result of lidocaine effect At the same time that conduction for these very early premature depolarizations is improving that for less premature depolarizations is depressed Hence, it appears that lidocaine might modify conduction of premature depolarizations by three mechanisms (1) the acceleration of repolarization and enhancement of conduction of very early premature depolarizations may normalize propagation of depolarizations that were previously decremental, (2) the depression of membrane responsiveness and V_{m} over a wide range of activation voltages may induce bidirectional block in segments of cardiac tissues in which unidirectional block and reentry were occurring, (3) although the effective refractory period decreases, its relative prolongation with respect to action potential duration results in protection against the propagation of premature depolarizations during a greater proportion of phase 3 repolarization than occurs during control

Kermaier and associates[6] have reported that lidocaine in therapeutic concentrations has no effect on the electrocardiographic P R, QRS Q T, or R R intervals in human subjects The results we observed on the canine ECG in this study were comparable, no changes occurring in these variables until higher drug concentrations were attained It might be argued that the effects of lidocaine we described with regard to conduction are incompatible with the maintenance of a normal electrocardiographic P R interval or QRS duration However, the slowing of conduction in the Purkinje fiber bundles was of small magnitude and might not necessarily be apparent in the ECG The degree of slowing was consistent with that reported by Sugimoto and associates[7] in their studies of lidocaine induced alterations of conduction in awake dogs These observations are also consistent with those of Rosen and asso

ciates [2] who observed that therapeutic concentrations of lidocaine either had no effect or slightly depressed intraventricular conduction in human subjects but did not accelerate it

In summary our studies indicate that lidocaine in concentrations that are consistent with clinical use exerts certain effects similar to those of procaine amide and other local anesthetics [6 13] on the electrophysiologic properties of Purkinje fibers While quantitative differences may exist between lidocaine and other local anesthetics with regard to time of onset duration and magnitude of effect the changes observed suggest that there are similarities in the mechanism of antiarrhythmic action

Summary

Effects of selected plasma lidocaine concentrations on the action potentials of isolated canine Purkinje fibers were studied with microelectrode techniques and a method for perfusing PF with the arterial blood of a normokalemic dog Lidocaine was administered to the donor as an intravenous injection of 0 5 to 2 0 mg per kilogram or as an intravenous infusion of 4 to 50 μg per kilogram per minute and plasma concentrations were determined by gas chromatography At plasma lidocaine concentrations from 0 2 to 9 9 μg per milliliter no significant changes in donor arterial pressure heart rate or electrocardiographic P R and QRS intervals occurred and Purkinje fiber resting membrane potential was unchanged Donor Q T intervals were unchanged at lower lidocaine concentrations (up to 4 0 μg per milliliter) and decreased at higher levels (4 1 to 9 9 μg per milliliter) Purkinje fiber AP changes commenced in 2 to 3 minutes of lidocaine injection At lower lidocaine levels AP amplitude maximum slope of phase 0 depolarization (V_m) AP duration and effective refractory period decreased membrane responsiveness was depressed and automaticity of spontaneously firing Purkinje fibers decreased These changes were accentuated at higher lidocaine concentrations Conduction usually was unchanged or slowed at lower plasma lidocaine levels and slowed at higher concentrations When ouabain intoxicated *preparations* were studied lidocaine exerted a depressant effect on the AP These studies indicate that the mechanisms whereby therapeutic lidocaine concentrations may modify arrhythmias are not unlike those of other local anesthetics and include depression of V_m membrane responsiveness and conduction

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Effects of coronary arteriography on atrioventricular conduction: Studies with His bundle electrography

Sachiyoshi Abe, M.D.
Masashi Itoh, M.D.
Tsutomu Kamei, M.D.
Kozo Ohyama, M.D.
Nobuhiro Kaseda, M.D.
Hiroshi Unakami, M.D.
Honjo, Japan

Despite the wide use of His bundle electrography, few studies have dealt with the effects of intracoronary injection of contrast material on A-V conduction.[1] A-V block and prolongation of the P-R interval on surface electrocardiograms (ECG) during selective coronary arteriography have suggested that injection of contrast material into the coronary arteries causes A-V conduction delay. Whether the delay is localized within the A-V node or in the His-Purkinje system can be determined with the use of His bundle electrography. In recent studies using this technique during coronary arteriography,[2] a prolonged A-H interval without any change in the H-V time was reported. However, no satisfactory explanation has so far been given on the mechanism of prolongation of the A-H time. The purpose of this paper is to present our results on comparing the effects of intracoronary injection of contrast material, normal saline solution, and hypertonic glucose solution. Osmotic effect of the contrast material is emphasized here.

Material and methods

His bundle recordings of 26 patients undergoing selective coronary arteriography, either for aortocoronary bypass surgery or for establishing the diagnosis of ischemic heart disease, were reviewed. Twenty-six patients, comprising 17 men and 9 women and ranging from 33 to 65 years of age, were studied. Arteriograms revealed normal or negligibly narrowed coronary arteries in 17 patients and significant occlusive disease in the remaining nine. There was no ECG evidence of A-V block in any of these patients.

The patients were premedicated with meperidine 35 mg with oral administration of 100 mg of pentobarbital sodium. The technique of Judkins[3] or Amplatz and associates[4] was employed for coronary arteriography, and opacification of the left coronary artery was followed by the right in each arteriographic study. After introduction of a catheter into the orifice of either main coronary artery, 6 ml. of normal saline solution was injected into the coronary artery before the injection of contrast material. A 8 ml. quantity of 76 per cent Urografin (a mixture of methylglucamine diatrizoate and sodium diatrizoate) was employed for opacification. During intracoronary injection of normal saline solution as well as the contrast material, continuous His bundle electrograms were recorded with a modification of the method of Scherlag and associates. In addition, in five patients other than the above 26 patients, 6 ml. of hypertonic (20 per cent) glucose solution was injected into the coronary arteries with continuous His bundle recordings after an arteriographic study for the purpose of comparing the effect of this solution on A-V conduction with that of the contrast material.

The arterial distribution pattern was deter-

From the Cardiology Division and the Departments of Medicine of the Yuri General Hospital, Honjo, Japan.

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Reprint requests: Sachiyoshi Abe, M.D., Yuri General Hospital, Cardiology Division, 38 Higashimachi, Honjo 015, Japan.

Table I A V conduction disturbances during coronary arteriography in 26 patients*

Case No	Age	Sex	Clinical diagnosis	Coronary arteriogram	Arterial distribution pattern	*Left coronary arteriography* A H before CAG (msec)	A H during CAC (msec)	Change in A H (%)	Effect on A V conduction	*Right coronary arteriography* A H before CAG (msec)	A H during CAG (msec)	Change in A H (%)	Effect on A V conduction
1	50	M	Angina	Normal	Right	90	90	0	None	94	132	40	Prolonged
2	50	F	Angina	Normal	Balanced	82	82	0	None	92	121	[illegible]	Prolonged
3	36	F	Angina	Normal	Balanced	72	72	0	None	70	93	33	Prolonged
4	33	F	Angina	Normal	Right	91	91	0	None	94	140	49	Prolonged
5	63	M	PAT	Normal	Left	98	124	27	Prolonged	104	104	0	None
6	[illegible]	F	Angina	Normal	Balanced	112	112	0	None	118	136	15	Prolonged
7	48	M	Angina	Normal	Right	122	122	0	None	122	156	28	Prolonged
8	[illegible]	M	Angina	CX occluded (90%)	Right	80	80	0	None	82	138	68	Prolonged
9	60	M	Angina	Multiple occlusive lesions	Right	98	98	0	None	102	146	43	Prolonged
10	62	M	Myocardial infarction	AD occluded (100%)	Balanced	102	102	0	None	112	132	18	Prolonged
11	54	F	Angina	Multiple occlusive lesions	Right	82	82	0	None	102	128	25	Prolonged
12	[illegible]	F	Angina	Multiple occlusive lesions	Right	96	96	0	None	98	124	27	Prolonged
13	61	M	Angina	Normal	Left	86	112	30	Prolonged	106	106	0	None
14	[illegible]	M	Angina	CX occluded (75%)	Right	80	80	0	None	74	140	[illegible]	Prolonged
15	[illegible]	F	Angina	Normal	Balanced	110	110	0	None	112	146	30	Prolonged
16	[illegible]	M	Angina	Normal	Right	98	98	0	None	130	164	26	Prolonged
17	41	F	Angina	Normal	Right	92	92	0	None	90	128	42	Prolonged
18	58	M	Angina	AD occluded (80%)	Right	102	102	0	None	110	154	40	Prolonged
19	60	M	Myocardial infarction	AD occluded (90%)	Right	88	88	0	None	114	134	18	Prolonged
20	52	F	Angina	Normal	Balanced	88	88	0	None	96	125	30	Prolonged
21	35	M	Angina	Normal	Right	82	82	0	None	88	136	55	Prolonged
22	40	M	Angina	Normal	Balanced	72	72	0	None	72	95	32	Prolonged
23	37	M	NCA	Normal	Balanced	104	104	0	None	124	182	47	Prolonged
24	62	M	NCA	Normal	Right	112	112	0	None	100	136	36	Prolonged
25	52	M	Angina	AD occluded (50%)	Left	94	126	34	Prolonged	102	102	0	None
26	41	M	NCA	Normal	Left	88	142	61	Prolonged	90	90	0	None

Abbreviations AD = anterior descending artery CAC = coronary arteriography CX = circumflex artery F = female M = male NCA = neurocirculatory asthenia PAT = paroxysmal atrial tachycardia

mined according to Schlesinger's[8] criteria of dominance with respect to the arterial supply to the A V node and the posterior interventricular surface of the heart

Results

In all 26 patients either left or right coronary injection of 76 per cent Urografin produced prolongation of the A H interval (Table I) The A H interval began increasing about 4 seconds after the initiation of injection reached its peak at an average of 7 7 seconds, and returned to the control level by 20 seconds (Figs 1 to 3) In all patients the duration of prolongation of the A H interval did not exceed 20 seconds as shown in Figs 1 to 3 The upstroke of A H prolongation
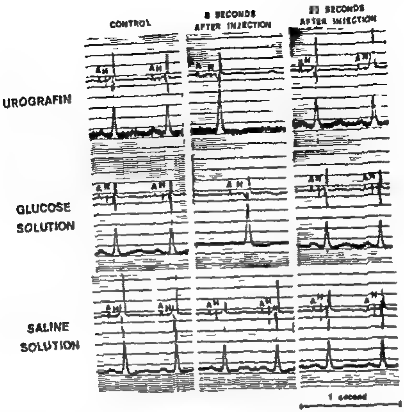
Fig 1 An example of the effects of right coronary arterial injection on the A H interval (case 29 right preponderance) His bundle electrograms and simultaneously recorded surface ECG s (Lead II) during coronary arteriography with 76 per cent Urografin following injection of 20 per cent glucose solution and normal saline solution.

curve was steeper than the downward slope in most patients The increase in the A H interval ranged from 15 to 68 per cent and the A H interval at peak prolongation (133 9 ± 18 7 [S D] msec) was significantly higher ($P < 0\,001$) than the control value (98.3 ± 15 7 msec) On the other hand no detectable change was noted in H V intervals following either left or right coronary arteriography

In four patients with left preponderance in arterial distribution pattern left coronary arteriography caused a prolongation of the A H interval while this interval did not change following right coronary opacification In the remaining 22 patients whose coronary distribution pattern showed either right preponderance or balanced distribution no change was produced by left coronary arteriography whereas prolongation of the A H interval resulted from right coronary injection of contrast material (Table I)

In contrast to the role of the arterial distribution pattern as described above the site of injection of the contrast material which produced an increased A H interval was not directly related to the sites of occlusive arterial lesion However it seemed that prolongation of the A H interval was more remarkable in patients with narrowed coronary arteries (Table I)

Following either left or right coronary arterial injection of 6 ml of normal saline solution no detectable changes were observed in His bundle electrograms in all 26 patients

In Table II the effects of intracoronary injection of hypertonic (20 per cent) glucose solution in an additional five patients are summarized The intracoronary injection of glucose solution in these patients showing either right coronary preponderance or balanced distribution pattern had a remarkably similar effect to that of 76 per cent Urografin on the A H interval More specifically injection of 20 per cent glucose solution into the left coronary arteries did not produce any prolongation of the A H interval whereas right coronary arterial injection invariably resulted in

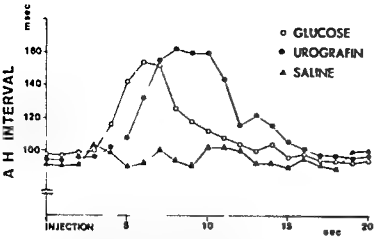

Fig 2 Effects on the A H interval of 76 per cent Urografin (filled circles) 20 per cent glucose solution (open circles) and normal saline (filled triangles) in the same patient Note prolonged A H interval resulting from intracoronary injection of Urografin and of glucose solution in contrast with unchanged A H interval following injection of normal saline

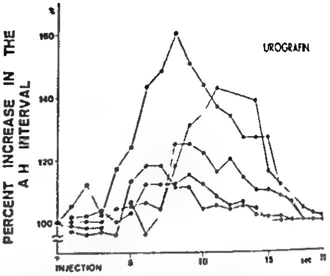

Fig 3 Effects of coronary arteriography with 76 per cent Urografin on the A H interval in five patients (cases 8 9 10 11 and 26)

Table II A V conduction disturbances following injection of glucose solution and of Urografin into the right coronary artery*

Case No	Age	Sex	Clinical diagnosis	Distribution pattern	*20 % glucose solution* A H before injection (msec)	2 A V block	A H after injection	Change in A H (%)	Duration of prolonged A H (peak) (sec)
27	47	F	VPB	Right	140	Yes	–	–	3 15 (4)
28	52	M	Myocardial infarction	Right	86	No	103	20	4 1 (6)
29	66	M	Angina	Right	96	No	154	60	3 15(C)
30	38	M	NCA	Right	124	No	164	32	4 14(5)
31	36	M	NCA	Balanced	94	No	133	41	3 16(5)

Abbreviations F = female M = male CAG = coronary arteriography NCA = neurocirculatory asthenia * A V block = second degree A V block VPB = ventricular premature beats

prolonged A H interval culminating in a second degree A V block in one patient (Table II) Following injection of 20 per cent glucose solution the pattern of increase in the A H interval was similar to that observed during coronary arteriography although the time course of the changes in the A H interval appeared more rapid with the injection of 20 per cent glucose solution than following the contrast material (Figs 1 to 4, and Table II)

Discussion

Selective opacification of the coronary arteries is accompanied by a variety of transient changes in surface ECGs These include sinus slowing prolonged P R intervals second degree heart block, premature beats ventricular tachycardia and fibrillation ST T changes changes in the mean QRS vector, and intraventricular hemiblock[7 11] The genesis of these changes has not been fully elucidated However MacAlpin and his co workers[7] postulated that these striking ECG changes produced by selective coronary injections were the results of differences in potential between areas of myocardial tissue perfused with contrast material and areas containing no contrast materials Some authors have assumed that chemical or toxic effect of the contrast

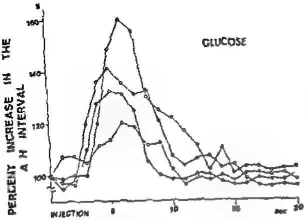

Fig 4 Effects of intracoronary arterial injection with 20 per cent glucose solution on the A H interval in four patients (cases 28 to 31)

76" Urografin				
A H before CAG (m ec)	*2 A V block*	*A H during CAG (msec)*	*Change in A H (")*	*Duration of prolonged A H (peak) (sec)*
13?	Yes	–	–	5 16(8)
86	No	109	?,	6-15( )
96	No	16?	69	5-1"(8)
1?0	No	163	36	6-18(6)
94	No	13?	45	5-1 ( )

material causes these ECG changes[8] Benchimol and McNally have suggested that myocardial ischemia associated with an appreciable dilution of the coronary blood by contrast agents is probably sufficient to cause various hemodynamic and ECG changes

With His bundle electrography it has been observed that intracoronary injection of contrast material causes prolonged A H interval without changing the H V time [2] As shown in our results we also confirmed that the A H interval became prolonged during coronary arteriography with the use of "6 per cent Urografin Prolongation of the A H interval started at about 4 seconds after the beginning of injection reached its maximum value (ranging from 115 to 168 per cent of the control) at 7 7 seconds and returned to the control level by 20 seconds Similar prolongation of the A H interval was also produced by an injection of 20 per cent glucose solution However it should be emphasized that intracoronary injection of normal saline solution of the same amount did not produce any change in the A H interval Furthermore there was a close interrelationship between the side of injection causing prolonged A H intervals and the coronary arterial distribution pattern Therefore prolongation of the A H interval is considered to be a result of perfusion of the A V nodal region with contrast material However Nakhjavan[1] reported that A H prolongation did not always correlate with injection into the vessel which gave origin to the A V node artery This is surprising in view of our results and we have no explanation for the discrepancy

Although various electrophysiologic alterations may accompany coronary arteriography in addition to delayed A V conduction the following discussion is restricted to factors causing prolongation of the A H interval Possible explanations for the prolonged A H interval observed during coronary arteriography are the following (1) chemical effect (2) hypoxia (3) parasympathetic effect and (4) osmotic effect

It was postulated that chemical or toxic effect of contrast materials might cause ECG changes including rhythm disturbances[8] Our results however showed that hypertonic glucose solution having no chemical property in common with the contrast material had a remarkably similar effect on A V (nodal) conduction Therefore it is unlikely that A V conduction delay results from a chemical effect of the contrast material

As is widely accepted hypoxia is a factor decreasing conductivity through its effect of decreasing the membrane potential and the maximal rate of phase 0 depolarization Hypoxia is considered to occur mainly from dilution of circulating blood by contrast material[8] Although hypoxia may also be expected to result from dilution or replacement of circulating blood with the injection of normal saline solution no A V conduction disturbances were observed in our study Therefore it is likely that A V nodal delay is not a result of hypoxia Another possible mech

anism producing hypoxia is coronary arterial spasm which can be seen following intracoronary insertion of a catheter or injection of contrast materials. Generally, however, such coronary arterial spasm occurs rather infrequently and at various locations and it lasts much longer (in the order of minutes). Hence, it seems quite unlikely that hypoxia due to arterial spasm would cause the transient nodal conduction delay of rather uniform pattern and of short duration (less than 20 seconds).

Nakhjavan emphasized the parasympathetic effect of contrast material on A V nodal conduction during coronary arteriography. Indeed it is generally accepted that the A V junction is innervated by efferent vagus and stimulation of cardiac vagus nerve results in A V conduction delay. Our data showed that delayed A V conduction during coronary arteriography was produced by perfusion of the A V node with the contrast material. Therefore if vagal reflex plays an important role in the delayed A V nodal conduction during coronary arteriography, it must be assumed that this parasympathetic reflex originates from afferent endings existing in the A V nodal area. However, no report has demonstrated parasympathetic receptors functioning in this area although many studies have shown parasympathetic receptors at various sites of the heart. It is not quite unlikely that the contrast material has a direct effect on the (efferent) nerve endings not through reflex, manifesting a cardiodepressing effect (as discussed below).

A discussion on osmotic effect is now in order. Our data showed that hypertonic (20 per cent) glucose solution, when injected into the coronary artery had an effect remarkably similar to that of 76 per cent Urografin on A V nodal conduction. Osmolality of the former is 1.3 Osm per kilogram of water while that of the latter is 1.9 Osm per kilogram of water, both at 20° C. It is quite unlikely that glucose has deleterious chemical effects on either the musculature or the nerve endings of the heart immediately after its solution is brought into contact with these tissues. Therefore, physical property of hypertonic glucose solution (hyperosmolality) may be responsible for the immediate prolongation of the A H interval following its intracoronary injection. Hypertonic solution injected into the coronary arteries would produce elevated intracapillary osmotic pressure and cause a shift of water from the extracellular space of the myocardial tissue into the capillaries. Thus, the concentration of extracellular potassium ions may be elevated. According to the Nernst equation, elevated extracellular K concentrations result in a reduced transmembrane potential. Thus the membrane potential may be reduced with the injection of hypertonic solution such as the contrast material and 20 per cent glucose solution. It is widely accepted that decreased conductivity of Purkinje fibers usually results from reduction in their transmembrane potential which is accompanied by decreased rising velocity (dV/dt) of phase 0 of the action potential. However it is uncertain whether the same argument would apply to the conductivity within the A V node. Watanabe and Dreifus have demonstrated in perfused rabbit hearts that elevated extracellular potassium concentrations predominantly depress conduction within the atria and the His Purkinje system whereas intra A V nodal conduction is either spared or ever protected by high potassium levels. Therefore one possible mechanism is that the high osmotic pressure of the contrast material or 20 per cent glucose acts on nerve endings in the A V node rather than directly on the nodal cell membrane, although the presence of such mechanism has not been proved in the present study. Indeed it has been believed that choline acetylase requires potassium ion as an activator and an increase of potassium therefore accelerates this synthesis thus tending to increase the cholinergic effect.[20] Hence it seems that cholinergic action can be potentiated by an increase of (extracellular) potassium in the A V node caused by osmotic effect of the contrast material leading to the delayed nodal conduction.

In summary it is suggested that prolongation of the A H interval during coronary arteriography may be resulted from potentiated cholinergic action in the A V node through the osmotic effect of the contrast material. This concept is also supported by the fact that no A V conduction disturbances are produced by intracoronary injection of isotonic saline solution.

Summary

The effect of coronary arteriography on atrioventricular (A V) conduction was studied in 26 patients with the use of His bundle electrography. Slowing of atrioventricular conduction (pro

longed A H interval) was observed in all 26 patients following either left or right coronary arteriography without a detectable change in the H V interval In four patients with left coronary preponderance in arterial distribution pattern prolonged A H interval was produced only by injecting the contrast material into the left coronary artery Conversely in the remaining 22 patients either with right preponderance or balanced distribution prolongation of the A H time was a result of opacification of the right coronary artery The A H interval at peak prolongation (133 9 ± 18 7 [S D] msec) was significantly higher than the control measurement (98 3 ± 15 7 msec) ($P < 0\ 001$) Prolongation of the A H interval started around 4 seconds after the initiation of injection reached its peak at an average of 7 7 seconds and subsided within 20 seconds When intracoronary injection of 6 ml of normal saline was made in these 26 patients no change was observed in the His bundle electrograms On the other hand hypertonic (20 per cent) glucose solution when injected into coronary arteries had an effect remarkably similar to that of contrast material on A V conduction These findings suggest that prolonged A H interval observed during coronary arteriography may be a result of osmotic effect of the contrast material rather than hypoxia resulting from dilution of coronary blood flow

We thank Yoshio Watanabe M D and Hiroshi Kato M D for their valuable help with this study We are also indebted to Machiko Kudo and Fumio Kato for their technical assistance

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Echocardiographic analysis of intracardiac anatomy in endocardial cushion defect

Yukio Komatsu, M D
Yasuo Nagai, M D
Minoru Shibuya, M D
Atsuyoshi Takao M D
Koshichiro Hirosawa M D
Tokyo Japan

Endocardial cushion defect (ECD) is derived from an underdevelopment of both the anterior and posterior endocardial cushion tissues in the atrioventricular canal which results in deformities and/or partial defects of the atrioventricular valves and the intracardiac septa[1-2] If we obtain echocardiographic information about each intracardiac constituent and their anatomic interrelation, this noninvasive technique could make it possible for us not only to diagnose ECD but also to assess the degree of the intracardiac anomaly A method of M mode scan introduced by Feigenbaum[3] may prove useful in studying the interrelation

Echocardiographic descriptions have already been reported in the literature,[4-8] but as yet no systematic analysis has been performed The purpose of this study is to analyze the intracardiac anatomy of ECD, using the echocardiographic techniques standardized by us and to define the limitations of those techniques

Method

Echocardiographic studies were performed in 13 patients with ECD ranging in age from 2 to 30 years Ten cases out of 13 were proved to be the incomplete form by both angiocardiography and operations The remaining three cases were confirmed ECD by angiocardiography, but they presented peculiar echocardiographic features different from those of the incomplete form As a result of echocardiographic scans, these cases were thought to have the free floating form of ECD

The examinations were carried out using an ultrasonoscope, Sanei Sokki Model UC 101B made in Japan This apparatus transmits and receives intermittent pulses of ultrasound at a frequency of 700 pulses per second and utilizes a 2MHz transducer probe of 16 mm diameter The echoes were displayed on an oscilloscope Tektronix Type 602 and were recorded on 35 mm film with an Asahi Pentax camera made in Japan

In order to obtain accurate anatomic information and to avoid an incomplete examination it was decided that a standard technique should be used to investigate ECD This consisted of two beam directions (1) and (2), and two M mode scans (3) and (4), as follows (1) the mitral beam direction (2) the tricuspid beam direction (3) the M mode scan between the mitral and tricuspid valves and (4) the M mode scan between the mitral and aortic valves The patients were placed in a supine position and the ultrasonic probe was applied to a small area of the anterior chest wall within the third or fourth intercostal space and within a few centimeters from the left parasternal border Mitral echoes were obtained in the posterior or posterior-slight lateral direction of the ultrasound beam, tricuspid echoes were obtained in the posterior medial direction, and aortic valvular echoes in the posterior medial superior direction The M mode scans were performed manually

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From the Heart Institute Japan Tokyo Women s Medical College 10 Kawada cho Shinjuku ku Tokyo Japan

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Reprint requests Koshichiro Hirosawa M D The Heart Institute Japan Tokyo Women s Medical College 10 Kawada-cho Shinjuku ku Tokyo Japan

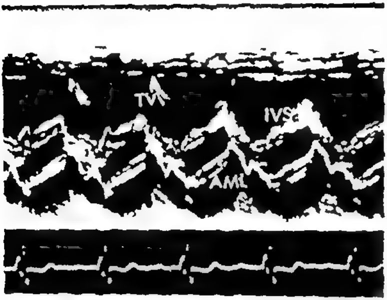


Fig 1A. Echocardiogram in the mitral beam direction The beam passes from the anterior mitral leaflet *(AML)* to *the posterior wall of the left atrium* A dilated right ventricle and a paradoxical motion of the interventricular septum (IVS) are characteristic of right ventricular volume overload Note the presence of the *tricuspid echoes* *(TV)* the systolic multiple echoes of the mitral valve and the prolonged mitral-septal apposition in diastole

mitral echoes followed that proposed by Edler and Gustafson[9]

Results

I Echocardiographic features of the incomplete form of ECD

A Echocardiograms in the mitral direction An initial step of the examination was to find mitral echoes Various patterns of the mitral valve were detected with slight changes of the beam direction even within the mitral direction and conversely they offered an exact recognition of the beam direction

When the beam passed from the mitral valve to the posterior wall of the left atrium (Figs *1A* and *1B*) the characteristic features were indications of right ventricular volume overload systolic multiple echoes of the mitral valve and simultaneous recording of the mitral and tricuspid valves These three features were found in every patient with the incomplete form of ECD When the beam passed the anterior mitral leaflet (Fig 1A) the echocardiogram showed predominantly indications of right ventricular volume overload an enlargement of the right ventricle and a paradoxical motion of the interventricular septum[10] The anterior mitral leaflet exhibited the prolonged mitral septal apposition in diastole which was described by Gramiak and Nanda[4] This feature was constantly obtained but was not specific to ECD It was very similar to that of atrial septal secundum defect However with or without moving the transducer echocardiograms characteristic of ECD could be obtained with repetitive examinations in the mitral direction (Fig *1B*) The mitral valve was seen as multiple echoes during systole There were usually more than two echoes which ended at the opening motion of the mitral valve In diastole the E point of the valve was superimposed on the interventricular septum Then either the anterior leaflet or the leaflet with a motion similar to the normal posterior leaflet motion (so called posterior leaflet) was recorded The registering of both leaflets simultaneously in diastole occurred in only one patient out of 10 Simultaneous recording of the mitral and tricuspid valves in the same beam direction was a constant finding The traces of the tricuspid valve were less continuous than those of the mitral valve The opening motion and early diastolic slope of the tricuspid valve could be easily recorded

When the beam was moved slightly laterally toward the apex and passed from the mitral valve to the posterior wall of the left ventricle the mitral echoes presented a specific pattern for ECD as shown in Fig 2 The mitral valve displayed multiple echoes with an abnormal

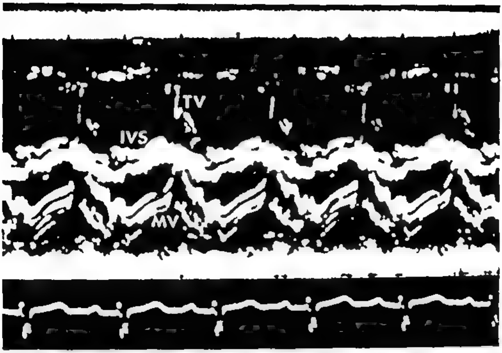


Fig 1B Echocardiogram in the mitral beam direction The beam passes from the mitral valve (MV) to the posterior wall of the left atrium The multiple systolic echoes of the mitral valve during systole and simultaneous recording of the mitral valve and the tricuspid valve (TV) are characteristic of ECD The trace of TV is less continuous than that of MV The diastolic motion of MV is somewhat distorted The features to show right ventricular volume overload are also included

round anterior motion during systole The most anterior echo was derived from the anterior leaflet this was verified by an M mode scan between the mitral and tricuspid valves The abnormal anterior motion in systole was more marked in the seven child patients than in the three adult patients The adult patients showed the same mitral pattern as presented in Fig 1 of the report by Williams and Rudd[4] In diastole only the so called posterior leaflet of the mitral valve was registered, without a trace of the anterior leaflet The pattern with the systolic multiple echoes and the diastolic so called posterior leaflet was demonstrable in every patient with the incomplete form of ECD We could presume a diagnosis of ECD when we obtained this feature The interventricular septum in this beam direction did not show a paradoxical motion

B Echocardiograms in the tricuspid direction When the transducer was rotated medially from the beam direction in which the mitral valve was recorded the tricuspid valve was easily recognized The valve occupied the anterior half of the cardiac chamber (Fig 3) The tricuspid valve had larger excursion than the mitral valve The interatrial septum which had already been studied by Matsumoto[11] in patients with atrial septal secundum defect, was identified in the posterior space of the valve in four patients but not in the remaining six patients It seemed difficult to obtain the interatrial septal echoes in patients with large ostium primum atrial septal defect

C M mode scans between the mitral and tricuspid valves An M mode scan between the mitral and tricuspid valves gave the most specific diagnostic echocardiographic feature which clarified the interrelation between the atrioventricular valves and the septa Fig 4 shows a typical echocardiogram In this figure, the mitral valve was recorded in the space posterior to the interventricular septum in the mitral beam direction, and the tricuspid valve in the space anterior to the septum in the tricuspid beam direction When the ultrasound beam was gradually moved from the mitral direction to the tricuspid direction the anterior mitral leaflet shifted anteriorly toward the interventricular septum and then became superimposed on it Subsequently, the echoes of the septum disappeared and the tricuspid valve separated from the superimposed echoes of the mitral valve and the septum Around the beam direction in which the valves and the septum interacted, the motion of the anterior mitral leaflet was clearly restricted and the tricuspid valve was registered partially usually in early

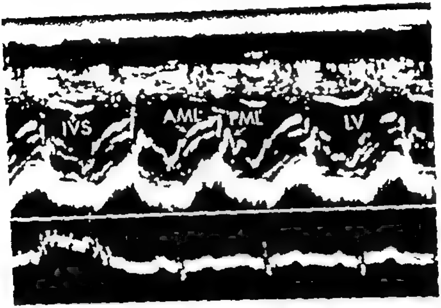


Fig 2 Echocardiogram in the mitral beam direction A typical echocardiogram of a patient with the incomplete form of ECD with the beam passing from the mitral valve to the posterior wall of the left ventricle The mitral valve shows systolic multiple echoes which have an abnormal round anterior motion and finish at the opening motion of the valve In diastole only the so called posterior mitral leaflet (*PML*) is recorded without a trace of the anterior leaflet

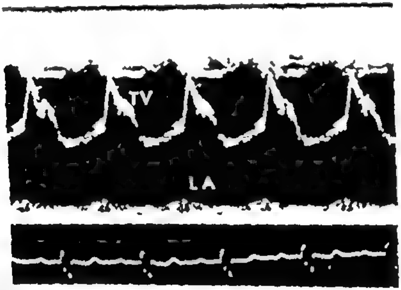


Fig 3 Echocardiogram in the tricuspid beam direction The tricuspid valve occupies the anterior space in the cardiac chamber The excursion of the valve is usually larger than that of the mitral valve The posterior space of the valve is the left atrium (*LA*) The interatrial septum is not recorded

diastole The echocardiogram in Fig 5 was taken in the beam direction in which the valves and the septum interacted with each other In systole the anterior mitral leaflet was just posterior and parallel to the interventricular septum The mitral echoes became the tricuspid echoes as soon as the opening motion of the mitral valve had begun In diastole the mitral valve was completely superimposed on the septum The interruption of the septal echoes just after the opening motion of the mitral valve was found in three patients

These findings which show the interaction

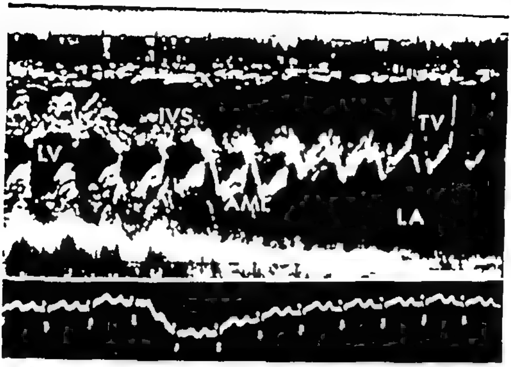


Fig 4 M mode scan between the mitral and tricuspid valves Rotating the transducer from the mitral direction (left) to the tricuspid direction (right) the anterior mitral leaflet shifts anteriorly and becomes superimposed on the interventricular septum Then the tricuspid valve separates from the superimposed echoes Around the beam direction in which the anterior mitral leaflet the interventricular septum and the tricuspid valve interact the motion of the anterior mitral leaflet is restricted and the opening motion of the tricuspid valve is identified These findings termed the mitral interventricular septal tricuspid (MVT) connection are specific to the incomplete form of ECD

between the atrioventricular valves and the interventricular septum, were obtained in every patient with the incomplete form of ECD They appear to be an echocardiographic representation of the attachment of the mitral and tricuspid valves on the crest of the interventricular septum which we have termed the 'mitral interventricular septal tricuspid (MVT) connection'

In the four patients in whom the interatrial septum was recorded the septal echoes were interrupted by the presence of the MVT connection and the continuity between the mitral valve and the septum was not observed

D M mode scans between the mitral and aortic valves The narrowing of the outflow tract of the left ventricle could be seen by using an M mode scan between the mitral and aortic valves (Fig 6) Rotating the transducer from the mitral valve to the aortic valve the interventricular septum became the anterior wall of the aorta at the same level but a difference in the level was found between the anterior mitral leaflet and the posterior wall of the aorta The anterior leaflet was displaced anteriorly and the distance between the D point of the anterior mitral leaflet and the interventricular septum was less than the *aortic diameter* This was thought to be an echocardiographic representation equivalent of the goose neck deformity in angiocardiography [1] The echocardiographic identification of the outflow tract narrowing of the left ventricle with the M mode scan was less sensitive than angiocardiography, but was clearly observed in five patients out of 10 When the beam passed the aortic valve an enlargement of the outflow tract of the right ventricle was also found

II Echocardiograms in the free floating form of ECD In the three patients with proved ECD by angiocardiography, echocardiographic features were quite different from those of the incomplete form as shown in Fig 7 In the tricuspid beam direction only a valve was recorded in the anterior space of the cardiac chamber Moving the beam toward the mitral direction, the interventricular septum appeared and the valve transversing the septum gradually shifted posteriorly In the mitral beam direction the valve occupied the posterior space of the septum The valve was continuous between the mitral and tricuspid beam directions and no restriction of the valvular motion which showed an interaction between the valve and the septum was observed From these echocardiographic findings it was thought that the r com

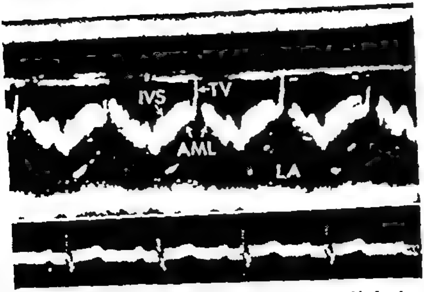
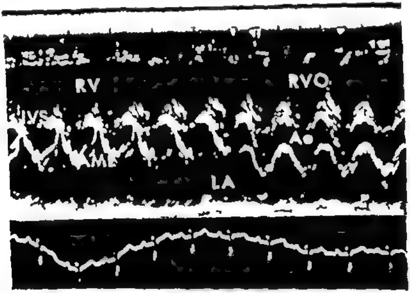


Fig 5 A typical echocardiogram in the beam direction in which the anterior mitral leaflet the interventricular septum and the tricuspid valve interact In systole the anterior mitral leaflet is just posterior and parallel to the interventricular septum The anterior mitral leaflet becomes the tricuspid valve as soon as the opening motion of the mitral valve has begun The interrup ion of the septum after the opening motion of the mitral valve is sometimes recorded in ECD In diastole the mitral valve is completely superimposed on the septum



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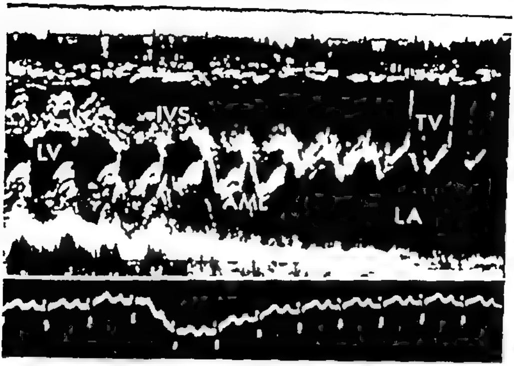
atrioventricular valve was *free floating* in the ventricles The anterior common atrioventricular valve had a much larger excursion than the anterior mitral leaflet of the incomplete form of ECD In the mitral beam direction the systolic valvular echoes were recorded as multiple echoes and the posterior common atrioventricular valve was observed as echoes moving posteriorly in diastole

Discussion

In order to analyze the intracardiac anatomy of ECD we took the mitral tricuspid and aortic valves as three reference points inside the body



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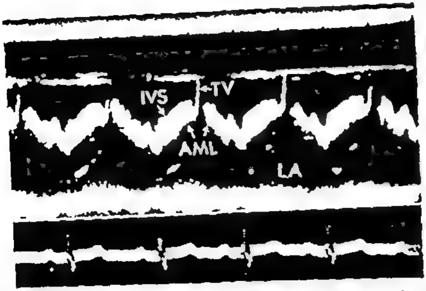

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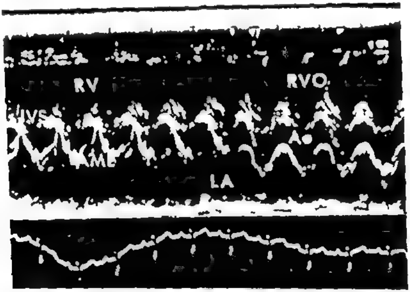

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Discussion

In order to analyze the intracardiac anatomy of ECD we took the mitral tricuspid and aortic valves as three reference points inside the body

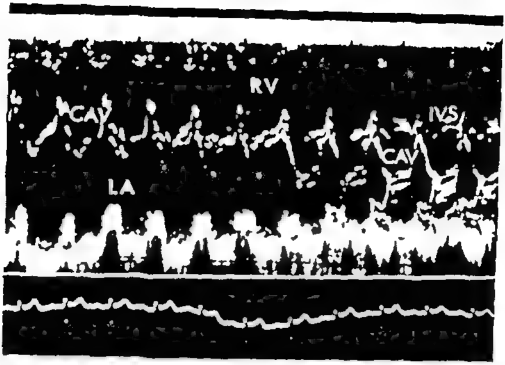

Fig 7 M mode scan in a patient with the free floating form of ECD The beam is moved from the tricuspid direction (left) to the mitral direction (right) The anterior common atrioventricular valve is located at the level anterior to the interventricular septum in the tricuspid direction and posterior to the septum in the mitral direction The valve with a large excursion is continuous between two beam directions No restriction of the valvular motion by the septum is observed The posterior common atrioventricular valve is recorded only in the mitral direction

Information about the mitral valve and the interventricular septum was obtained in the mitral beam direction those of the tricuspid valve and the interatrial septum in the tricuspid direction Therefore, by scanning between three reference points it was possible to analyze the interrelation between the atrioventricular valves the intracardiac septa, and the aorta Based on anatomy and our experiences we finally chose these two beam directions and two M mode scans as a standard technique for echocardiographic examination for ECD Williams and Rudd[4] reported that optimal mitral echoes may not be displayed in patients with ECD This seems to be due to the various patterns of the mitral valve produced by minute changes of the beam direction In our experience it was easy to register the mitral echoes Although the intracardiac orientation differed from patient to patient even when a transducer was placed at the same point on the chest wall the most important thing was to procure the optimal beam direction and plane for each patient by using pictures on an oscilloscope With experience it was possible to make a diagnosis within 15 to 20 minutes We are convinced that an analysis using a combination of multiple beam directions and planes as described above is indispensable for echocardiographic examinations of various congenital heart diseases An adequate combination for each cardiac anomaly remains to be determined

The echocardiographic feature of the MVT connection could be explained by the anatomic background of the mitral and tricuspid valves attached to the crest of the scooped interventricular septum This feature was thought to be specific to both the incomplete form and type II of the complete form as described in the classification by Tenckhoff and associates[11] Also it indicated the presence of atrial septal primum defect and anterior displacement of the anterior mitral leaflet Nimura and associates[6] using ultrasound tomography, described the echocardiographic feature of atrial septal primum defect as being a discontinuity between the mitral valve and the interatrial septum On an M mode scan taken between the mitral and tricuspid valves in patients with atrial septal secundum defect, the interventricular septum became the tricuspid valve and the anterior mitral leaflet became the interatrial septum On the other hand in the patients with ECD the anterior mitral leaflet became superimposed on the interventricular septum and connected to the tricuspid valve The

interatrial septum was either not recorded or if recorded was interrupted by the anterior mitral leaflet Williams and Rudd[5] found a feature similar to our MVT connection and described it as an echocardiographic equivalent of the angio cardiographic goose neck deformity

The systolic multiple echoes of the mitral valve sometimes consisted of more than two parallel echoes The mitral cleft could be one of the causes or the deformity of the mitral valve might have more than one surface from which to reflect the ultrasound as the beam covers a somewhat wide area of the valve It was difficult to explain the systolic multiple echoes as evidence of the cleft

If the mitral cleft exists the posterior segment of the anterior mitral leaflet is anatomically continuous with the posterior mitral leaflet and therefore it would be possible for it to move in the same manner as the posterior leaflet Because it is impossible to distinguish one from the other echocardiographically we called the mitral echoes moving posteriorly in diastole the so called posterior mitral leaflet

For diagnosis and treatment it is important to know whether the ventricular septal defect is present or not Unfortunately our technique could not provide this information

Pieroni and associates[3] and Williams and Rudd have reported that the anterior common atrioventricular valve in patients with the complete form of ECD had a large excursion which moved into the right ventricle during dias tole and into the left ventricle during systole Our results were consistent with theirs However they did not clarify the spacial orientation of the valve and the interventricular septum To diag nose the free floating form of ECD echocardio graphically we think the following items should be satisfied (1) to show the presence of the interventricular septum (2) to show that a single anterior atrioventricular valve is continuous between the mitral and tricuspid beam directions and its motion is not restricted by the interven tricular septum (3) to show that the valve occu pies the anterior position of the interventricular septum in the tricuspid direction and the posterior position of the septum in the mitral direction and (4) to show that the valve has a large excursion

Recently Sahn and associates have reported the usefulness of multiple crystal echocardiog raphy for establishing the diagnosis of ECD It has the advantage of evaluating cross sectional cardiac anatomy in real time An improvement of the echocardiographic apparatus will facilitate the noninvasive clinical diagnosis of congenital heart diseases

Summary

A standard echocardiographic technique was proposed for an analysis of the intracardiac anatomy of endocardial cushion defect (ECD) It consisted of two beam directions mitral and tricuspid and two M mode scans between the mitral and tricuspid valves and between the mitral and aortic valves Using this technique echocardiographic studies were performed on 13 patients with ECD including 10 patients with the incomplete form and three patients with the free floating form

In patients with the incomplete form an M mode scan between the mitral and tricuspid valves showed the specific features of the interac tion between the mitral valve the interventric ular septum and the tricuspid valve termed the mitral interventricular septal tricuspid (MVT) connection The systolic multiple echoes and the diastolic echoes of the so called posterior leaflet of the mitral valve were constant findings in the mitral direction The tricuspid valve although less continuous was recorded simultaneously with the mitral valve in the same direction Anterior displacement of the anterior mitral leaflet was shown on an M mode scan between the mitral and aortic valves giving an echocardio graphic representation of the angiocardiographic goose neck" sign Evidence showing the pres ence of right ventricular volume overload was also found

In patients with the free floating form an anterior common A V valve with a large excur sion was recorded on an M mode scan between the mitral and tricuspid valves The valve was located posterior to the interventricular septum in the mitral direction and anterior to the septum in the tricuspid direction There was no finding to show the interaction between the valve and the septum The posterior common A V valve was registered only in the mitral direction

Our technique made it possible to diagnose ECD using a noninvasive echocardiographic method and discriminate the free floating form from other forms of ECD

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Rate of change of ventricular power
An indicator of ventricular performance during ejection

Paul D. Stein, M.D.
Hani N. Sabbah, B.S.
Oklahoma City, Okla.

A variety of indices of ventricular performance have been developed and utilized with considerable success. Many of these are based upon the measurement of intraventricular pressure and its first or second derivatives during the isovolumic phase of contraction.[1-4] During the isovolumic period, pressure is related to tension along the ventricular wall as shown by the Laplace equation. Therefore, isovolumic indices which measure combinations of ventricular pressure and its derivatives have the advantage of reflecting ventricular wall tension in an uncomplicated fashion. A disadvantage is the fact that performance is evaluated on the basis of information derived prior to the period during which useful work is performed. It would be appealing, therefore, to evaluate ventricular performance during ejection. Several important indices of performance during ejection, of course, have been utilized. These include cardiac output,[5] ventricular work,[5] ventricular power,[5] ventricular ejection rate,[6] and, in more recent years, rate of change of flow,[7] velocity of circumferential fiber shortening,[8] and ejection fraction. These are all useful and contribute prominently to the evaluation of the cardiac performance of patients. Even so, these indicators of cardiac function have shortcomings which warrant the continued exploration of methods for the evaluation of ventricular performance.[9]

In the present study, an attempt was made to develop an expression for the evaluation of ventricular performance that would have the following characteristics: It would be free of assumptions, would have fluid dynamic as well as physiological meaning, and would reflect alterations of the inotropic state, yet be relatively independent of alterations of preload and afterload. It is likely and even desirable that such an expression would incorporate component hemodynamic terms which previously have been shown to relate to ventricular performance. In this respect, the expression would serve in an integrative fashion. An expression indicative of the rate of change of ventricular power during ejection was derived. Its derivation, theoretical basis, and ability to reflect ventricular performance will be discussed.

Methods

Theoretical considerations. One can measure power generated by the ventricle during ejection as the product of intraventricular pressure and aortic flow:

$$\text{Power} = p \cdot Q \qquad (1)$$

where p = intraventricular pressure (dynes · cm^{-2}) and Q = aortic flow (cm^3 · sec^{-1}).

The instantaneous rate of change of power (dynes · cm · sec^{-2}) is obtained by differentiation of Equation 1 and is calculated as follows:

$$\text{Rate of change of power} = Q\frac{dp}{dt} + p\frac{dQ}{dt} \qquad (2)$$

where p and Q are defined as in Equation 1, dp/dt = rate of change of pressure (dynes · cm^{-}

From the Department of Medicine, University of Oklahoma College of Medicine, and Veterans Administration Hospital, Oklahoma City, Okla.

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Reprint requests to: Paul D. Stein, M.D., Veterans Administration Hospital, 921 N.E. 13th St., Oklahoma City, Okla. 73104.

sec⁻¹), and dQ/dt = rate of change of flow (cm³ sec⁻²)

Studies in dogs The rate of change of ventricular power during ejection, as well as standard ejection indices of performance were studied during drug induced alterations of the contractile state and during alterations of the preload and afterload Eighteen healthy mongrel dogs weighing 16 to 29 kilograms, were studied All dogs were anesthetized with sodium pentobarbital (23 to 26 mg per kilogram) and studied with the chest open Respiration was maintained by a Harvard Apparatus Company respirator (Millis Mass) attached to a cuffed endotrachial tube

Left ventricular and aortic pressures were measured simultaneously with two catheter tip micromanometers (Millar Instruments Inc Houston Texas) appropriately positioned under fluoroscopic control Catheter tip pressure sensors were calibrated with a mercury manometer before each study and baseline levels were confirmed at the end of the study All dogs received heparin 2 5 mg (per kilogram of body weight) in order to avoid the accumulation of fibrin at the tip of the catheter Left ventricular end diastolic pressure was measured immediately after the A wave or when this was absent on the downstroke of the R wave of the electrocardiogram (ECG) which usually corresponded to the onset of the rapid ascent of pressure

Pressures were recorded on a photographic recorder at a paper speed of 200 mm per second The pressures were manually digitized at 1 mm (0 005 sec) intervals Appropriate corrections were made for minor variations of the paper speed Equations descriptive of left ventricular pressure were calculated by the Chebyshev polynomial approximation technique with the aid of a Hewlett Packard HP 2100A computer (Hewlett Packard Cupertine, Calif) Usually a fifth degree polynomial equation satisfactorily described the left ventricular pressures during the isovolumic period Any points from the computed data that disagreed by 10 per cent or more from the measured data were discarded Such points were almost always at the initial portion of the curves Most portions of the curves were within 3 per cent of the digitized data From the computed mathematical equations descriptive of intraventricular pressure, the instantaneous first derivative of pressure was calculated at 5 msec intervals throughout the isovolumic period and during ejection until peak ejection was reached Two or more beats were analyzed during control periods and following each intervention, and the results were averaged

Aortic flow was measured with a Biotronex Laboratory Inc (Silver Spring Md) cuff electromagnetic flow transducer placed around the root of the aorta Zero flow was defined as the level of the diastolic flow just prior to the rapid upstroke of flow during ejection[11] Aortic flow transducers were calibrated by simultaneous measurements in duplicate of cardiac output by the indicator dilution technique with indocyanine green Aortic flow was recorded at a paper speed of 200 mm per second and manually digitized in a fashion identical to that of left ventricular pressure Similarly, equations descriptive of aortic flow were calculated by the Chebyshev polynomial approximation technique From these equations instantaneous values of aortic flow and the rate of change of flow were calculated at 5 msec intervals With the aid of a computer, instantaneous values of power and the rate of change of power were also calculated at 5 msec intervals, in accordance with Equations 1 and 2 *

The effects of a drug induced augmentation of the contractile state were observed in nine dogs during the infusion of isoproterenol at a rate of 3 8 μg per minute Following a recovery period of 20 minutes the effects of a drug induced reduction of the contractile state were observed following the intravenous injection of 4 to 5 mg of propranolol

The effects of an augmentation of the afterload and of the preload were studied in nine dogs In this series of studies, left ventricular end diastolic volume was measured in addition to the various hemodynamic variables Left ventricular end diastolic volume was calculated by the single plane area length method,[12] with 35 mm cine at 40 frames per second during the injection of 10 cm³ of sodium and meglumine diatrizoates (Hypaque M—75 per cent) Amplification was determined by utilization of a two dimensional scale which also permitted compensation for any roentgenographic distortion (Such distortion was negligible) Only the first four beats of each injection were analyzed to avoid alterations of contractility that may have occurred due to contrast material passing through the coronary circulation Care

* Analog systems are now being developed to facilitate these calculations

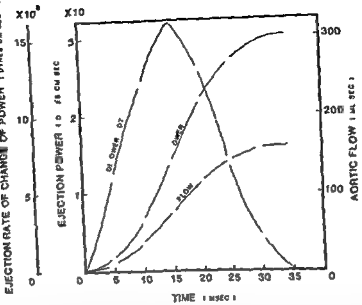

Fig 1 Instantaneous values of aortic flow ventricular power and the rate of change of ventricular power [d (power)/dt] during the early portion of ejection Time after the onset of ejection is shown. Power reaches a peak coincident with peak flow The rate of change of power reaches a peak earlier in the ejection period and is virtually zero at the time of peak flow

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A recovery period of 20 minutes was allowed after all injections of contrast material Following this control pressures heart rate and flow were remeasured and shown to be unchanged from initial values Subsequently interventions were introduced which altered the afterload or preload Pressures and flow were remeasured Then a ventriculogram was again performed for the recalculation of left ventricular end diastolic volume Pressures and ventriculograms were performed within 3 minutes of each other

The effects of an augmented afterload were studied in nine dogs The afterload was increased by a constant infusion of angiotensin amide—5 7 μg per minute in one dog and 11 5 μg per minute in eight dogs During the infusion of angiotensin the average aortic systolic pressure increased from 150 ± ▮ to 181 ± ▮ mm Hg (mean ± ▮E) and the average aortic diastolic pressure increased from 115 ± 5 to 142 ± 6 mm Hg ($P < 0.001$) (Table III) This elevation of the afterload caused only minor and statistically insignificant changes of the heart rate and end diastolic volume

An increased preload was induced in nine dogs by the rapid intravenous injection of 300 cm of 6 per cent dextran 75 in normal saline (McGraw Laboratories Glendale Calif) which corresponded to a dose of 12 to 16 cm^3 per kilogram of body weight (Eight of these dogs previously received angiotensin one previously received isoproterenol A period of recovery of 20 minutes was allowed following all prior studies) The duration of the injection of dextran was 2 to 4 minutes Following these infusions of dextran 75 the left ventricular end diastolic pressure increased from 8 ± 1 to 13 ± 1 mm Hg ($P < 0.001$) and left ventricular end diastolic volume increased from 48 ± 2 to 67 ± 6 cm^3 ($P < 0.01$) (Table IV)

Results

The rate of change of power reached a peak value during the early portion of ventricular ejection (Fig 1) Minimal values occurred at the onset of ejection and at peak aortic flow

During states of augmented contractility instantaneous values of the rate of change of power were higher than control values at any instantaneous value of aortic flow (Fig 2) Similarly a reduction of the contractile state was accompanied by a fall of the rate of change of power at all levels of flow (Fig 2)

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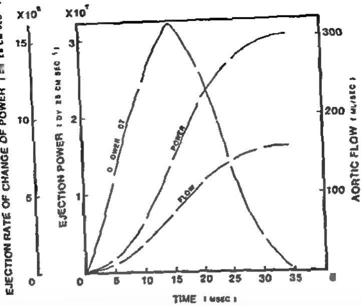

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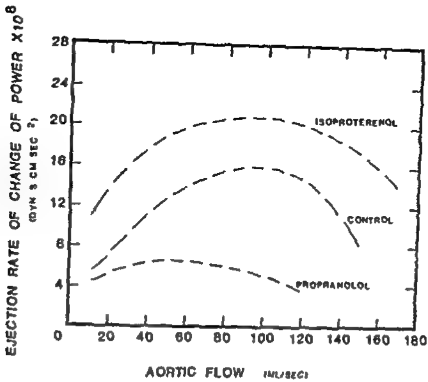

Fig 2 Instantaneous values of the rate of change of ventricular power shown at various levels of aortic flow At all levels of flow comparable values of the rate of change of power reflect higher states of contractility

Table I Effects of isoproterenol

Dog No	Aortic BP (mm Hg)		LVFDP (mm Hg)		Heart rate (beats/min)		Cardiac output (L/min)		Stroke volume (cm /beat)		Peak flow (cm /sec)		Peak dQ/dt (cm /sec)		Peak power × 10 (dynes—cm sec ⁻¹)		Peak d(power)/dt×10ⁿ (dynes—cm sec)	
	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I
1	130/110	132/104	6	2	193	218	3 1	5 0	16	23	280	400	7 100	9 600	4 8	6 2	13	17
2	102/87	95/74	9	7	160	200	1 2	1 3	7	[illegible]	110	140	3 000	5 600	1 4	1 7	4	8
3	96/67	94/60	8	7	144	160	2 7	2 1	18	13	130	160	3 600	5 000	1 3	2 1	4	6
4	108/77	110/78	12	11	170	184	1 1	1 0	6	5	100	130	3 500	3 900	1 3	1 8	4	6
5	137/113	130/100	10	10	152	158	3 5	3 3	23	21	230	250	7 200	7 800	4 1	4 3	13	14
[illegible]	147/121	132/100	11	11	193	204	1 9	2 4	10	14	160	210	8 000	10 000	3 1	4 0	16	21
7	115/96	132/95	6	8	176	200	1 9	2 7	11	13	170	210	8 200	9 000	2 3	3 0	13	15
8	156/128	140/122	12	7	129	160	2 6	4 4	20	27	310	400	10 400	16 000	6 2	8 1	2?	35
9	124/100	133/95	19	[illegible]	194	200	1 2	1 4	6	7	100	150	2 700	5 200	1 3	2 4	4	9
Mean	124/100	122/92	10	8	168	187	2 1	2 6	13	14	180	230	6 000	8 100	2 9	3 7	10	15
±S E	7/7	6/6	1	1	8	8	0 3	0 5	2	3	30	40	900	1 300	0 6	0 7	2	3
Probability		NS/<0 01		NS		<0 01		NS		NS		<0 001		<0 01		<0 01		<0 01

C Control I isoproterenol

During the infusion of isoproterenol the peak rate of change of ventricular power increased from (10 ± 2) × 10ⁿ to (15 ± 3) × 10ⁿ dynes cm sec ⁻² (mean ± S E) (P < 0 01)* (Table I) Following the injection of propranolol the peak rate of change of ventricular power diminished to (6 ± 1) × 10ⁿ dynes cm sec ⁻² (P < 0 001) (Table II) Peak flow, peak power, and the peak rate of change of flow also showed prominent and statistically significant changes in association with these drug induced alterations of the contractile state (Tables I and II)

Augmentation of the afterload caused no significant change of the peak rate of change of power Control values (12 ± 3) × 10ⁿ dynes cm sec ⁻² were comparable to values following the in

* Paired t test

Table II Effects of propranolol

Dog No	Aortic BP (mm. Hg)		LVEDP (mm Hg)		Heart rate (beats/min)		Cardiac output (L/min)		Stroke volume (cm /beat)		Peak flow (cm /sec)		Peak dQ/dt (cm /sec)		Peak power $\times 10^{7}$ (dynes–cm. sec)		Peak d(power)/dt $\times 10^{8}$ (dynes–cm sec)	
	C*	P*	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
1	130/110	120/190	6	2	193	142	3.1	2.5	16	18	280	250	7,100	5,200	4.8	4.0	13	10
2	102/87	74/67	9	7	160	176	1.2	0.9	7	7	110	80	3,000	2,000	1.4	0.7	5	2
3	96/67	79/63	8	9	144	132	2.7	2.6	18	20	130	80	3,600	2,100	1.3	0.8	4	2
4	108/77	98/74	12	6	170	138	1.1	0.8	6	6	100	100	3,500	3,300	1.3	1.2	4	4
5	137/113	141/113	10	10	152	123	3.5	3.3	23	30	230	220	7,200	6,000	4.1	3.7	13	10
6	147/121	133/109	11	17	193	145	1.9	1.4	10	10	160	140	8,000	3,800	3.1	2.2	16	7
7	115/96	110/80	6	8	176	136	1.9	2.1	11	15	170	160	8,200	4,800	2.3	2.1	13	7
8	156/128	112/92	[illegible]	27	129	120	2.6	2.2	20	18	310	220	10,400	7,000	6.2	3.8	22	12
9	146/121	133/113	6	8	160	150	1.3	1.0	10	10	85	64	2,300	1,900	1.4	1.0	4	3
Mean	126/102	111/88	9	10	164	135	2.1	1.8	13	15	175	146	5,900	4,000	2.9	2.2	10	6
± SE	7/7	8/7	1	2	7	3	0.3	0.3	2	3	27	23	1,000	600	0.6	0.5	2	1
Probability		<0.01/<0.01		NS		<0.001		<0.01		NS		<0.02		<0.01		<0.01		<0.001

C, Control P, propranolol.

Table III Effects of afterload

Dog No	Aortic BP (mm. Hg)		LVEDP (mm Hg)		LVEDV (cm)		Heart rate (beats/min)		Cardiac output (L/min)		Stroke volume (cm /beat)		Peak flow (cm /sec)		Peak dQ/dt (cm. /sec)		Peak power $\times 10^{7}$ (dynes–cm sec)		Peak d(power)/dt$\times 10^{8}$ (dynes–cm sec)	
	C*	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A
1	157/119	180/147	11	10	45	41	206	203	1.9	2.0	9	10	130	130	5,900	6,500	2.6	3.0	12	16
2	115/94	140/115	9	9	31	30	136	137	1.6	1.6	12	12	110	90	3,100	2,800	1.7	1.7	5	5
3	142/102	177/124	8	8	–	–	176	179	3.5	3.5	20	19	190	200	6,000	5,800	3.6	4.8	12	14
4	177/141	194/164	6	8	56	[illegible]	169	171	1.3	1.3	8	8	150	160	6,100	5,400	3.1	3.9	13	13
5	163/124	208/161	9	13	45	54	141	126	1.0	1.6	7	12	100	120	3,600	4,300	1.7	3.5	6	12
6	168/129	172/146	9	11	36	40	111	170	1.3	1.5	12	13	160	170	5,300	4,300	3.0	3.7	11	11
7	151/101	177/130	6	7	45	42	169	174	4.7	4.7	28	27	330	310	14,200	13,500	7.0	7.1	31	29
8	137/107	190/140	6	9	47	45	179	167	2.1	2.3	11	10	160	180	4,800	5,600	2.6	5.6	11	13
9	146/121	191/154	6	9	50	57	160	156	1.3	1.4	10	10	90	100	2,300	3,300	1.4	2.4	5	8
Mean	150/115	181/142	8	9	45	47	160	159	2.0	2.2	13	13	160	160	5,700	5,700	3.0	4.0	12	[illegible]
± SE	6/5	6/6	1	1	2	3	9	9	0.4	0.4	2	2	20	20	1,200	1,000	0.6	0.6	3	[illegible]
Probability		<0.001/<0.001		0.05		NS		NS		<0.05		NS		NS		NS		<0.02		NS

C Control A, Afterload.

creased afterload $(13 \pm 2) \times 10^{8}$ dynes cm ^{2} (Table III) Peak power in contradistinction to the peak rate of change of power did reflect the augmented afterload (Table III) Neither peak flow nor the peak rate of change of flow changed significantly following the increased afterload

The peak rate of change of power showed statistically insignificant changes after augmentation of the preload Control values of the peak rate of change of power were $(12 \pm 3) \times 10^{8}$ dynes-cm sec ^{2} after the preload was increased it was $(16 \pm 4) \times 10^{8}$ dynes cm sec ^{2} (Table IV) The average peak rate of change of flow increased 48 per cent but this change was not statistically significant (Table IV) Both peak flow and peak power showed definite and statistically signifi

Table IV Effects of preload

Dog No	Aortic BP (mm Hg) C*	Aortic BP (mm Hg) P	LVEDP (mm Hg) C	LVEDP (mm Hg) P	LVEDV (cm) C	LVEDV (cm) P	Heart rate (beats/min) C	Heart rate (beats/min) P	Cardiac output (L/min) C	Cardiac output (L/min) P	Stroke volume (cm /beat) C	Stroke volume (cm /beat) P	Peak flow (cm /sec) C	Peak flow (cm /sec) P	Peak dQ/dt (cm³/sec²) C	Peak dQ/dt (cm³/sec²) P	Peak power × 10 (dynes-cm sec) C	Peak power × 10 (dynes-cm sec) P	Peak d(power)/dt × 10 (dynes-cm sec) C	Peak d(power)/dt × 10 (dynes-cm sec) P
1	152/119	158/12[illegible]	11	14	[illegible]	46	206	174	1 9	2 8	9	16	130	180	5 900	6 400	2 6	4 0	12	14
2	115/91	136/9[illegible]	9	16	31	[illegible]	136	12[illegible]	1 6	2 0	12	16	110	150	3 100	4 600	1 7	2 8	5	9
3	142/102	150/102	8	11	—	—	176	174	3 5	4 7	20	27	190	230	6 000	7 000	3 6	4 6	12	14
4	177/141	159/131	6	12	56	79	169	196	1 3	2 0	8	10	150	170	6 100	5 400	3 1	4 0	13	12
5	163/124	131/108	9	12	[illegible]	59	141	143	1 0	3 1	7	22	100	160	3 600	5 900	1 7	3 6	6	13
6	151/101	153/113	[illegible]	14	48	68	169	200	4 7	6 2	28	31	330	400	14 200	30 000	7 0	7 1	31	47
7	168/129	143/120	9	16	[illegible]	104	111	139	1 3	2 6	12	19	160	220	5 300	4 800	3 0	4 7	11	10
8	134/11[illegible]	132/103	4	[illegible]	18	6[illegible]	[illegible]	150	2 1	2 7	13	18	110	180	3 300	7 400	2 0	3 2	6	13
9	137/107	152/116	6	17	[illegible]	68	179	1[illegible]2	2 1	3 1	10	20	160	180	4 800	5 200	3 0	4 0	11	11
Mean	149/115	146/113	8	13	48	67	160	163	2 2	3 2	13	20	160	210	5 800	8 500	3 0	4 2	12	16
± SE	6/5	4/4	1	1	2	6	9	9	0 4	0 5	2	2	20	30	1 100	2 700	0 5	0 4	3	4
Probability		NS/NS	<0 001		<0 01			NS	<0 001		<0 001		<0 001			NS	<0 001			NS

C Control P Preload

cant increments following the increased preload

The peak rate of change of power was linearly related to the peak rate of change of aortic flow (r = 0 99) This close correlation was observed during states of both augmented and reduced contractility (Fig 3)

Discussion

There were no assumptions implicit in the derivation of the equation descriptive of the rate of change of ventricular power during ejection The expression was derived on the basis of firm principles of fluid dynamics Obviously, ventricular outflow and intraventricular pressure must be accurately measured Since cuff flow transducers placed around the aorta fail to measure the portion of ventricular outflow that enters the coronary circulation an approximation is introduced in this measurement

The peak rate of change of power was responsive to drug induced alterations of the contractile state yet unresponsive to changes of afterload, it was affected little by changes of the preload With the exception of the peak rate of change of flow none of the other hemodynamic indices of performance that were measured during ejection showed such a response

The peak rate of change of power, although more complex in its measurement than the peak rate of change of flow, has advantages which recommend its utilization These are its fluid dynamic basis, its physiological meaning and its integrative characteristics The rate of change of power indicates an acceleration of energy expended upon the production of useful work by the ventricle during ejection Since fluid dynamic systems are comprehensively described on the basis of considerations of the energy of the system, it is likely that the acceleration of energy expenditure might be a useful expression

A particularly advantageous feature of the rate of change of ventricular power is the encompassing character of the expression It implies information related to ventricular work ventricular power, ventricular pressure, aortic flow, the rate of change of ventricular pressure, and the rate of change of ventricular flow Both ventricular power and ventricular work can be derived from the expression by integration Ventricular pressure aortic flow, and their respective rates of change are components of the expression Each of these expressions has been utilized previously for the evaluation of ventricular performance[1-7]

The instantaneous relations between myocardial force, velocity and fiber length are said to describe the contractile state of cardiac muscle

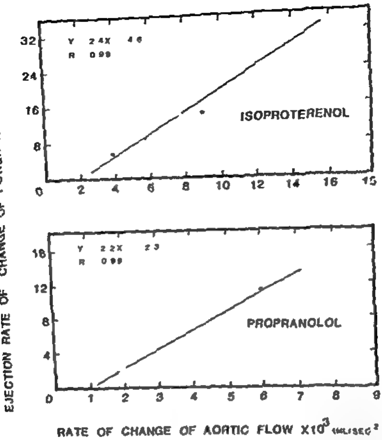

Fig 3 Peak rate of change of ventricular power shown in relation to the peak rate of change of aortic flow A linear relation was observed both during infusions of isoproterenol (top) and following propranolol (bottom)

preparations and these mechanical concepts have been applied to the intact heart and found to be useful Tension velocity length relations have been constructed for the human ventricle [4] It may be useful to know how the expression derived in this study of the rate of change of power relates to this previous work Although the relation is complex the rate of change of power can be written in terms of the length tension and velocity of muscle shortening This is possible because tension is related to pressure by the Laplace equation and circumferential fiber length and the velocity of fiber shortening are related to flow The exact relation depends upon the shape of the ventricle The rate of change of power written in terms of tension length and velocity of shortening in the particular case of an assumed spherically shaped ventricle is shown in Appendix I

The rate of change of power can be applied to the evaluation of patients during cardiac catheterization Instantaneous aortic velocity (as well as ventricular pressure) can be measured with a catheter tip sensor By assuming the profile of flow to be flat and the cross sectional area of the aorta constant the velocity signal would be identical with a flow signal [1] The essential parameters of the instantaneous rate of change of power therefore can be obtained

The rate of change of power is an expression of physiological meaning that can also be applied to the isovolumic period [17] Its form and derivation differ from the ejection rate of change of power since no flow occurs during the isovolumic period The concept of an acceleration of energy expenditure has meaning however during both the isovolumic phase of systole and the ejection phase and a useful evaluation of ventricular performance in patients has also resulted from the former [18]

Summary

An expression representative of the rate of change of ventricular power during ejection was

Table IV Effects of preload

Dog No	Aortic BP (mm Hg)		LVEDP (mm Hg)		LVEDV (cm)		Heart rate (beats/min)		Cardiac output (L/min)		Stroke volume (cm³/beat)		Peak flow (cm³/sec)		Peak dQ/dt (cm /sec)		Peak power × 10⁷ (dynes-cm sec)		Peak d(power)/dt × 10⁹ (dynes-cm sec)	
	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
1	152/119	158/12[illegible]	11	14	4[illegible]	46	206	174	1 9	2 8	9	16	130	180	5 900	6 400	2 6	4 0	19	14
2	11[illegible]/94	136/9[illegible]	9	16	31	3[illegible]	136	125	1 6	2 0	12	16	110	150	3 100	4 600	1 7	2 8	5	9
3	142/102	150/102	[illegible]	11	–	–	176	174	3 5	4 7	20	27	190	230	6 000	7 000	3 6	4 6	19	14
4	177/141	159/131	[illegible]	12	56	79	169	196	1 3	2 0	8	10	150	170	6 100	5 400	3 1	4 0	13	19
5	163/124	131/109	9	12	4[illegible]	59	141	143	1 0	3 1	7	22	100	160	3 600	5,900	1 7	3 5	6	13
6	151/101	1[illegible]3/113	6	14	48	68	169	200	4 7	6 2	29	31	330	400	14 200	30 000	7 0	7 1	31	4[illegible]
7	168/129	143/120	[illegible]	16	5[illegible]	104	111	139	1 3	2 6	12	19	160	220	5 300	4 800	3 0	4 7	11	10
8	134/115	132/103	4	8	49	6[illegible]	15[illegible]	150	2 1	2 7	13	18	110	180	3 300	7 400	2 0	3 2	6	13
9	137/107	152/116	[illegible]	17	50	68	179	162	2 1	3 1	10	20	160	180	4 800	5 200	3 0	4 0	11	11
Mean	149/115	146/113	[illegible]	13	48	67	160	163	2 2	3 2	13	20	160	210	5 800	8 500	3 0	4 9	19	16
± SE	6/5	4/4	1	1	2	6	9	9	0 4	0 5	2	2	20	30	1 100	2 700	0 5	0 4	3	4
Probability		NS/NS	<0 001		<0 01			NS	<0 001		<0 001		<0 001			NS	<0 001			NS

C Control P Preload

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Discussion

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A particularly advantageous feature of the rate of change of ventricular power is the encompassing character of the expression It implies information related to ventricular work ventricular power ventricular pressure aortic flow, the rate of change of ventricular pressure, and the rate of change of ventricular flow Both ventricular power and ventricular work can be derived from the expression by integration Ventricular pressure aortic flow, and their respective rates of change are components of the expression Each of these expressions has been utilized previously for the evaluation of ventricular performance [1 3 7]

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derived The primary advantages of the expression are its theoretical value and its ability to characterize ventricular performance The rate of change of ventricular power, measured during ejection, is virtually free of assumptions It has a fluid dynamic as well as a physiological meaning It serves in an integrative fashion by combining terms previously shown to be of functional significance Studies in dogs show that it reflects alterations of the inotropic state yet is relatively independent of alterations of preload or afterload In nine dogs isoproterenol caused the peak rate of change of power to increase from (10 ± 2) × 10^6 to (15 ± 3) × 10^6 dynes cm sec^{-2} (mean ± S E) (P<0 01) Propranolol produced a reduction from (10 ± 2) × 10^6 to (6 ± 1) × 10^6 dynes cm sec^{-2} (P <0 001) An increased afterload induced by angiotensin caused no change of the peak rate of change of power Augmentation of the preload with dextran, which caused a 40 per cent increase of the end diastolic volume, produced a statistically insignificant increase of the peak rate of change of power from (12 ± 3) × 10^6 to (16 ± 4) × 10^6 dynes cm sec^{-2} The rate of change of ventricular power, measured during ejection therefore appears to be a useful and meaningful indicator of ventricular performance that has many desirable characteristics

Appendix I

The rate of change of ventricular power during the ejection phase of systole can be expressed in terms of the tension, length, and velocity of muscle fiber shortening Any configuration of ventricular geometry can be assumed For simplicity of calculation, assume that the ventricle has a spherical configuration with a thin wall

According to the Laplace equation

$$p = \frac{2T}{r} \qquad (1A)$$

where T = tension (dynes/cm), p = pressure (dynes /cm ^{2}) and r = radius (cm)

Differentiating the Laplace equation

$$\frac{dp}{dt} = \frac{2}{r}\frac{dT}{dt} - \frac{2T}{r}\frac{dr}{dt} \qquad (2A)$$

If the ventricle is assumed to be spherical, its volume will be

$$Q = 4/3\,\pi r^3 \qquad (3A)$$

Flow can be obtained by differentiating Equation 3A

$$\dot{Q} = \frac{dQ}{dt} = 4\pi r^2 \frac{dr}{dt} \qquad (4A)$$

Since the rate of circumferential fiber shortening = $2\pi\,dr/dt$, flow can be considered as the product of 2 r^2 and circumferential fiber shortening rate The rate of change of flow is obtained by differentiating Equation 4A

$$\frac{dQ}{dt} = 8\pi r \left(\frac{dr}{dt}\right)^2 + 4\pi r^2 \frac{d^2r}{dt^2} \qquad (5A)$$

Now the rate of change of power, as derived in the text is

$$\text{Rate of change of power} = p\frac{dQ}{dt} + Q\frac{dp}{dt} \qquad (6A)$$

Therefore substituting Equations 1A, 2A, 4A and 5A in Equation 6A

$$\text{Rate of change of power} = 8\pi\left[rT\frac{d^2r}{dt^2} + r\frac{dr}{dt}\frac{dT}{dt} - T\left(\frac{dr}{dt}\right)^2\right]$$

It is shown therefore that for a ventricle of spherical configuration with a thin wall the ejection rate of change of power is a function of tension, fiber length, rate of fiber shortening and acceleration of fiber shortening

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patients with a prosthetic aortic valve (Cutter Smeloff) No time delay was detected between the mechanical closure on the echogram and the closing click on the phonogram of the prosthesis (Fig 1 *B*) In addition no time delay was observed in the onset of A_2 when simultaneous intracardiac and extracardiac phonograms were compared

In all cases five cardiac cycles were measured Only those cardiac cycles that showed good quality motion of both aortic valve cusps with clearly defined points of coaptation at end systole were used The interval (C A) from the point of coaptation (C) of the aortic cusps at end systole to the onset of A_2 was measured in each cycle to the nearest 5 msec (Fig 2)

Simultaneous recordings of aortic valve echogram left ventricular (LV) pressure central aortic pressure and intracardiac phonocardiogram were obtained in 3 additional subjects during diagnostic cardiac catheterization at a paper speed of 200 mm per second A No 8 French catheter with a distally located micromanometer (Millar Instruments Houston Texas) was passed retrograde through a brachial arteriotomy and positioned in the left ventricle A second catheter (No 5 French Millar Microtip) was passed percutaneously through the femoral artery and placed in the ascending aorta just above the aortic valve The high fidelity transducers were calibrated by a predetermined electronic calibration constant and equal calibration of the two signals was assured by simultaneous recording of aortic pressure with transducers

Results

The distribution of the C A_2 interval in the 125 cardiac cycles measured followed a bell shaped curve pattern (Fig 3) 58 cycles had an interval of 10 msec., 47 cycles had an interval of 15 msec and the remainder were distributed at intervals below 10 or above 15 msec A similar distribution pattern was observed when the total number of cycles was divided into normal and patient groups The average C A interval for the entire 125 cycles was 11 48 ± 0 38 msec (mean ± 1 S D) for the normal group C A_2 averaged 10 10 ± 0 37 msec and for the patient group it averaged 12 34 ± 0 36 msec Fig 4 shows examples of the C A intervals in 5 different subjects ranging from 0 to 15 msec

In 3 additional subjects simultaneous LV and central aortic pressures aortic valve echogram and phonocardiogram were recorded during cardiac catheterization An example of one of the 3 cases is shown in Fig 5 In all 3 cases A coincided with the incisura of the central aortic pressure Coaptation of the aortic valve cusps (C) occurred 8 msec prior to A_2 in the example in Fig 5 In the other 2 cases C A_2 measured 0 and 10 msec respectively The interval between the LV and

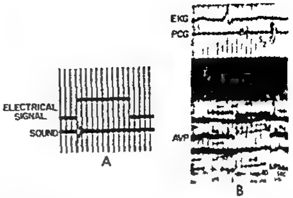

Fig 1 *Panel A* An electrical sound producing signal was introduced into the sound recording system No time delay between the onset of the sound and the electrical signal can be appreciated (paper speed, 200 mm /sec time lines 20 msec) *Panel B* Echogram of a prosthetic valve (*A V P*) with simultaneous external phonocardiogram (*PCG*) shows no delay between the closing of the AVP on the echogram and the closing click (*S*) on the PCG (Paper speed 100 mm /sec time lines 40 msec.)

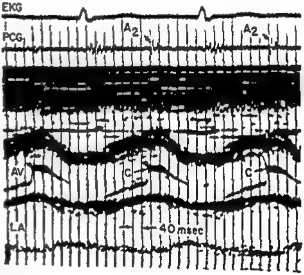

Fig 2 Aortic valve echogram (*A V*) with simultaneous phonocardiogram (*PCG*) and electrocardiogram (*EKG*) Coaptation of the aortic valve cusps (*C*) precedes onset of aortic component of second heart sound (*A*) The C-A interval was measured to the nearest 5 msec *LA* Left atrium

Aortic valve closure echocardiographic, phonocardiographic, and hemodynamic assessment

Pantelis C Anastassiades, M D
Miguel A Quinones M D
William H Gaasch M D
Ajit V Adyanthaya, M D
Alan D Waggoner
James K Alexander, M D
Houston Texas

The temporal relationship between the closure of the aortic valve and the aortic component of the second heart sound (A_2) has been a subject of controversy The commonly held view is that aortic valve closure is the cause for the origin of A [1,2] However different investigators, who used various techniques have de emphasized the part played by the aortic valve [3-5] Echocardiography allows virtually instantaneous delineation of intracardiac events Combining this technique with simultaneous phonocardiography and high speed photographic recording we have re examined the temporal relationship of aortic valve closure to A_2

Methods

Twenty five subjects without evidence of aortic valve disease were studied Ten (ages 14 to 64 years) had no evidence of organic heart disease (normal) The other 15 subjects (ages 21 to 64 years) suffered from various cardiac conditions Four had coronary artery disease 5 had nonrheumatic mitral valve disease, and 6 had idiopathic congestive cardiomyopathy Patients with aortic valve disease or paradoxical splitting of the second heart sound were excluded from the study

From the Department of Medicine Baylor College of Medicine and Ben Taub General Hospital Hou ton Texas

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Reprint requests Miguel A Quinones M D Department of Medicine Cardiology Division Baylor Colleg of Medicine 1200 Moursund Ave Houston Texas 77025

All subjects had electrocardiographic evidence of sinus rhythm without intraventricular conduction defects An electrocardiogram phonocardiogram and aortic valve echogram were simultaneously recorded on an Electronics for Medicine DR 8 multichannel recorder Tracings were taken at a paper speed of 100 mm per second with time intervals of 40 msec The phonocardiogram was recorded from the second intercostal space at the left sternal border, with the use of a piezoelectric microphone over a frequency of 50 to 500 Hz To eliminate the possibility of time delay occurring in the sound recording system, the system was tested by introducing into the microphone a sound signal with two metal bars which upon contact with each other, produced an electrical signal No time delay between the onset of the sound and the electrical signal was observed at paper speed up to 200 mm per second (Fig 1 *A*) The aortic valve echogram was obtained with a Smith Kline Ekoline 20 Ultrasonoscope utilizing a 2 25 MHz 0 5 inch transducer focused at 5 cm with a repetition rate of 1 000 impulses per second The transducer was placed at the third or fourth intercostal space to the left of the sternum aiming posteromedially to the anterior leaflet of the mitral valve and subsequently rotated cephalo medially until the anterior and posterior walls of the aorta together with echoes from the aortic valve cusps were identified To verify that ultrasound and audible sound from a single physical event in the cardiac cycle were simultaneously represented recordings were made from 3

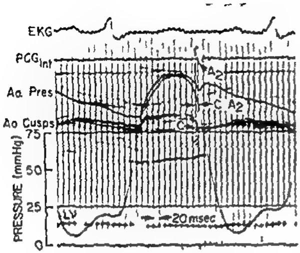

Fig 5 Simultaneous recordings of left ventricular (*LV*) and central aortic pressure (*Ao Pres*) intracardiac phonogram (*PCG int*) electrocardiogram (*EKG*) and aortic valve echogram (*Ao Cusps*) are illustrated A coincides with the incisura of the Ao Pres. The interval between the point of coaptation of the aortic valve cusps (*C*) and the onset of A_2, the C A interval is 8 msec The interval between LV and Ao Pres at the level of the incisura is 15 msec

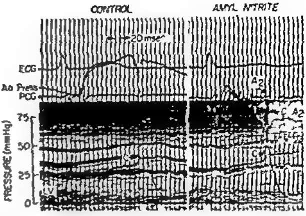

Fig 6 Simultaneous recordings of the left ventricular (*LV*) and central aortic pressure (*Ao Pres*) intracardiac phonogram (*PCG*) and electrocardiogram (*ECG*) are illustrated No appreciable interval between the point of coaptation of the aortic cusps (*C*) and the onset of A ($C A_2$) is shown in the control panel. The interval between the LV and Ao Pres at the level of the incisura (hangout interval) is 10 msec After administration of amyl nitrite (right band panel) a fall in the arterial pressure is accompanied by prolongation of C A to 8 msec and of the hangout interval to 20 msec

msec and by the development of a measurable $C A_2$ of 8 msec

Discussion

As early as 1915 Wiggers postulated a noiseless approximation of the semilunar valves, and that after vibrations of the closed valves and aortic blood column were responsible for the second heart sound Data which suggested that aortic valve closure occurs prior to the onset of the second heart sound were presented in 1962 by Criley and associates[5] who used cineangiographic studies in man and by Spencer and Greiss[7] who used simultaneous pressures (left ventricular and aortic) and aortic blood flow in open chest anesthetized dogs In 1964 MacCanon and co investigators applied a special electrical conducting device to time the relationship between aortic valve closure and the aortic incisura in the closed chest anesthetized dog Their data showed that the onset of the second heart sound occurred at the time of the aortic pressure incisura but was preceded by aortic valve closure The time interval between aortic and ventricular pressures at the level of the incisura (mean = 9 8 msec range from 5 to 13 msec) was the same as the interval from contact closure to the second heart sound In 1966 Piemme Barnett and Dexter[9] studying closed chest anesthetized dogs found that the onset of the second heart sound occurred approximately 25 msec before the nadir of the central aortic flow at a time when forward central aortic blood flow was still occurring These findings led them to conclude that A_2 occurs prior to closing of the aortic valve

Using cardiac echography in man we have demonstrated that the coaptation of the aortic cusps precedes the aortic component of the second heart sound the time interval between the two the $C A_2$ interval is variable ranging from 0 to 20 msec —an average of 11 5 msec Analysis of simultaneous pressure sound and aortic valve motion in 3 patients indicates that the $C A_2$ is an integral part of the hangout interval Shaver and associates[6] have suggested that the hangout interval reflects the opposition to forward flow, or impedance of the arterial tree This thesis was based on previous observations in man by Martin and associates[10] who found a lengthening of the hangout time during infusion of isoproterenol (a drug that causes a reduction in the resistance as well as an increase in the capacitance of the systemic arterial tree) and a shortening of this interval to almost zero during the infusion of Neo Synephrine (a drug that causes an increase in the resistance and a decrease in the capacitance

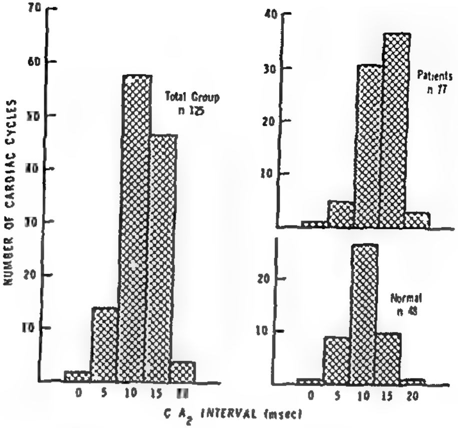

Fig 3 The distribution of the C A_2 interval in the total group (left hand panel) follows a bell shaped curve pattern Mean C A_2 ± standard deviation = 11 48 ± 0 38 msec A similar distribution pattern of C A_2 is observed when the total group is separated into "patient" and "normal" (right hand panel)

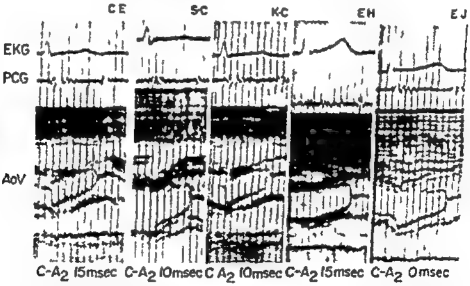

Fig 4 Examples of C A interval in 5 different subjects ranging from 0 to 15 msec *EKG* Electrocardiogram *PCG* Phonocardiogram *AoV* Aortic valve echogram (Paper speed 100 mm /sec time lines 40 msec)

aortic pressures at the level of the incisura, the hangout interval,* ranged from 8 to 20 msec in the [illegible] cases (15 msec in the case of Fig 5) The gradient between the aorta and left ventricle at the time of coaptation (C) was about 4 mm Hg

* A purely descriptive term suggested by Shaver and associates to define the time interval between the aortic incisura and left ventricular pressure at the level of the incisura

A recording from the subject in whom no measurable C A was observed is shown in Fig 6 (Control) The hangout interval was 10 msec After control measurements amyl nitrite inhalation was administered As shown in Fig 6, a significant fall in arterial blood pressure occurred during inhalation of amyl nitrite, and was accompanied by prolongation of the hangout time to 20

Case reports

Postmyocardial infarction (Dressler's) syndrome: Report of a case with immunological and viral studies

Harold L. Kennedy, M.D.*
Seattle, Wash.
Sunil K. Das, M.D.**
Ann Arbor, Mich.

The postmyocardial infarction syndrome (PMIS) initially described by Dressler[1] is of unknown etiology. Hypersensitivity reaction with autoimmunologic abnormality is most frequently invoked to explain the clinical syndrome of chest pain, fever, and polyserositis which typically has a tendency to recurrence. Laboratory evidence of inflammation and autoantibodies are cited in support of this view.[2] More recently, the possibility of viral infection has received renewed interest with the demonstration that viruses can remain dormant for long periods of time, later giving rise to clinical syndromes.[3]

It is the purpose of this report to describe a case of PMIS with results of immunologic and viral studies obtained prior, during, and after therapy of a typical acute exacerbation. In addition, recent modification of etiologic considerations will be reviewed.

Methods

Standard hematologic techniques were employed. Serum protein and immunoelectrophoresis were done according to accepted techniques.[4] Quantitative immunoglobulins, C_3 complement and C_4 complement were done by radial immunodiffusion techniques with kits obtained respectively from Phizer Diagnostics Division of Clifton, N. J., Hyland Laboratories of Costa Mesta, Calif., and Custom Reagent Laboratory of San Diego, Calif. Total hemolytic complement activity was measured by a 50 per cent lysis end point (CH_{50} units) of 5×10^7 sheep red blood cells per milliliter incubated for 40 minutes at 37° C.[6] Normal values for serum total hemolytic complement in our laboratory range from 80 to 160 CH_{50} per milliliter. The antinuclear antigen test was done according to methods modified from Gonzalez and Rothfield[7] and Barnett.[8] DNA binding was performed by a modified version of techniques described by Pincus and co-workers. The IgM rheumatoid factor test was performed according to the latex fixation method of Singer.[10] Absolute lymphocyte count was performed on the sedimentation buffy coat layer of blood according to standard hematologic techniques. Lymphocyte cultures were prepared for transformation studies according to the method of Rudolph, Mickelson, and Thomas.[11] Standard phytohemagglutinin and pokeweed stimulation methods were used. An immunofluorescent staining method adapted from Arsenberg and Block[12] was used to detect lymphocyte surface IgG globulin. Intradermal skin tests were performed in the standard manner.

An indirect immunofluorescent technique was employed to detect heart antibody according to the method of Kaplan, Meyersenan, and Kushner.[3] Left ventricular tissue was obtained from infants who died of noncardiac causes. Sarcolemma isolated from dog heart muscle was similarly used as an antigen in the immunofluorescent method.

Coxsackie and cytomegalovirus cultures and

From the Department of Medicine, Division of Cardiology, University of Washington, United States Public Health Service Hospital, Seattle, and the Department of Medicine, Division of Cardiology, University of Michigan Medical Center, Ann Arbor.

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Reprint requests to: Harold L. Kennedy, M.D., Department of Cardiovascular Services and Clinical Investigations, U.S. Public Health Service Hospital, Baltimore, Md. 21211.

of the arterial tree) In another study, Kumar and Luisada[11] reported significant prolongation of the hangout time in patients with aortic stenosis, a finding that was attributed to increased compliance of the poststenotic dilated aorta The development of a measurable C A interval in one of our cases subsequent to the inhalation of amyl nitrite in association with prolongation of the hangout time, suggests that the C A_2 interval not only is temporally related to the hangout interval, but also responds to changes in the impedance of the arterial tree in a similar manner This phenomenon may account for the variability of the C A interval among different subjects

Thus our data suggest that A_2 is not caused by coaptation of the aortic cusps per se but by physical events that occur at the time of or slightly after, coaptation

Summary

The temporal relationship between the closure of the aortic valve (AoV) and the onset of the aortic component of the second heart sound (A) was defined by simultaneous recording of AoV echogram, phonocardiogram (PCG), and electrocardiogram in 25 subjects Ten subjects had no heart disease (normal) 15 suffered from various cardiac conditions other than AoV disease (patients) The point of coaptation (C) of the AoV cusps to the onset of A_2, the C A_2 interval was measured to the nearest 5 msec in 125 cycles Fifty eight cycles had a C A of 10 msec and 47 cycles had a C A_2 of 15 msec The remainder were distributed at intervals below 10 or above 15 msec The average C A interval was 11 48 ± 0 38 msec (mean ± 1 S D) A similar distribution pattern was observed when the total number of cycles was divided into normal and patient' groups

In 3 subjects simultaneous equisensitive (catheter tip micromanometer) left ventricular and central aortic pressures PCG and AoV echograms were recorded C A_2 ranged from 0 to 10 msec , the interval between left ventricular and aortic pressure at the level of the incisura–hangout interval–ranged from 8 to 20 msec Inhalation of amyl nitrite in one subject produced a significant fall in arterial pressure accompanied by prolongation of the hangout interval from 10 to 20 msec and of the C A_2 interval from 0 to 8 msec Thus, the C A_2 interval is an integral part of the hangout time

Data suggest that A does not originate from the coaptation of the aortic valve cusps per se but is related to events that occur at the time of or slightly after coaptation

We wish to thank Dr J Michael Criley for his advice and encouragement

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Table I Humoral immunological studies

Study	*12/18/72*	*2/21/73*	*3/6/73*	*4/13/73*
Serum protein electrophoresis	Normal	Normal	Normal	Normal
Serum immunoelectrophoresis	Normal	Normal	Normal	Normal
Serum quantitative immunoglobulins	–	–	–	Normal
Total hemolytic complement	95	14?	–	9?
C complement†	–	100	–	99
[illegible] complement‡	–	496	–	–
Autoantibodies	–	–	–	–
ANA	Negative	Negative	–	Negative
DNA binding test	Normal	Normal	–	Normal
IgM rheumatoid factor	Negative	Negative	–	Negative
Whole heart muscle and sarcolemma	–	Positive	Weakly positive	Weakly positive

Normal total hemolytic complement = 80 to 160 CH_{50} units
†Normal C omplement = 100 to 200 mg per cent
‡Normal C complement = 3?7 to 674 mg per cent

Table II Cellular immunological studies

Study	*12/18/72*	*2/21/73*	*3/6/73*	*4/13/73*
Absolute lymphocyte count (mm)	1950	3775	2625	2550
Percentage of lymphocytes with surface IgG globulin	16%	37%	10%	11%
Lymphocyte transformation†				
Phytohemagglutinin stimulated	Normal	Normal	Moderate‡ decrease	Normal
Pokeweed-stimulated	Normal	Normal	Slight‡ decrease	Normal
Skin tests				
Histoplasmin	Negative			
Coccidioidin	Negative			
Intermediate strength PPD	Negative			
Mumps	Positive			

Control ra[illegible] 10 t 28 per c nt of ll lymphocyte cells
†Transformation studies d ne in autol gous serum
‡Cultures also done in control serum indicated th depressi n of response was related to a serum f tor probably steroid

matic without any medications immunologic studies and delayed hypersensitivity skin tests were performed On Feb 1 19 3, the patient noted an insidious onset of pleuritic chest pain and arthralgia Typical symptoms and signs of PMIS prompted hospitalization on Feb 21 1973 Studies were then obtained in serial fashion during the exacerbation of PMIS Following a trial of salicylate therapy alone and combined salicylate and indomethacin therapy prednisone th rapy was reinitiated with a prompt abatement of symptoms and a decreasing sedimentation rate Following a return of the sedimentation rate to normal, and three weeks of empiric low dose prednisone to avoid rebound phenomena medication was discontinued without recurrence of symptoms. The patient has remained asymptomatic to the present time

Results

Immunological studies (Tables I and II) performed when the patient was asymptomatic without medication on Dec 18 1972 revealed normal findings During PMIS exacerbation on Feb 21 1973 studies disclosed (Table I) serum circulating autoantibodies to whole heart muscle and sarcolemma particulate antigen as detected by indirect immunofluorescence Intense sarcolemmal and moderately intense subsarcolemmal types of staining were noted when whole human heart was used as the antigen (Fig 3) Similarly, intensely positive staining along the sarcolemmal margins were observed when the antigen used was dog heart sarcolemma Prior adsorption of the positive serum with human whole heart muscle powder human skeletal muscle powder or lyophylate of dog heart sarcolemma completely abolished positive immunofluorescence Prior adsorption with liver powder did not alter subsequent positive immunofluorescence tests In addition cellular immunologic studies (Table II) showed a moderate increase in the absolute

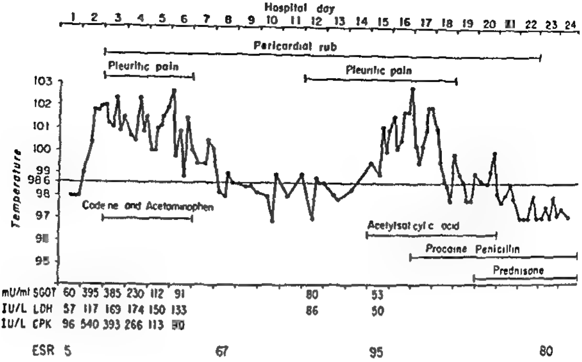

Fig 1 Admission hospital course of patient W S

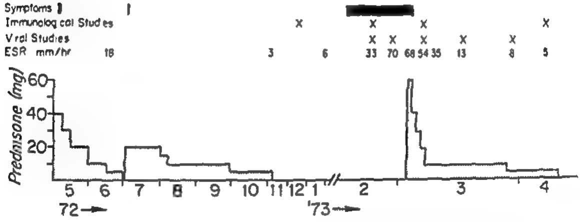

Fig 2 Follow up course of patient W S during the year of 1972 and 1973

coxsackie neutralizing antibody titers were performed in the clinical virology laboratory of Dr C George Raye at the University of Washington with methods previously described [11] All other viral studies were performed by the Seattle King County Laboratory Seattle Wash, and the Center for Disease Control Atlanta, Ga

Case report

Patient W S a 51 year old white male previously in good health developed spontaneous substernal chest pain and was admitted to the coronary care unit of the United States Public Health Service Hospital in Seattle Wash on April 6 1972 Physical examination on admission was essentially normal Laboratory studies revealed normal serum enzymes and Westergren sedimentation rate (ESR) An electrocardiogram at the time of admission was interpreted as evolving inferior myocardial infarction Portable chest roentgenogram revealed the transverse cardiac diameter to be within normal limits Typical serial electrocardiographic patterns and serum enzymes indicated inferior myocardial infarction with lateral extension over the succeeding days On the third hospital day the patient developed a sharp inspiratory left sided pleuritic pain and a triphasic pericardial rub

The patient s hospital course is indicated in Fig 1 Pleuritic pain was initially treated with codeine and acetaminophen with relief but subsequent recrudescence on the twelfth hospital day followed by temperature elevation and pulmonary infiltrates resulted in salicylate and procaine penicillin therapy The diagnosis of PMIS was made following an appreciation of a sedimentation of 95 millimeters of mercury and a chest roentgenogram interpreted as left lower lobe consolidation left pleural effusion and an increase in cardiac size Subsequent prednisone therapy resulted in a prompt defervescence of temperature a sense of well being gradual loss of pericardial friction rub and diminution of left pleural effusion

Fig 2 indicates the patient s course over the succeeding year On Dec 18 1972 with the patient well and asympto

Discussion

The *autoimmune etiology* of PMIS was initially considered when Dressler[13] suggested that antigens produced by myocardial necrosis lead in susceptible persons to the formation of autoantibodies which cause the syndrome. Participation of an immune mechanism in this syndrome was consistent with the latent period, the clinical manifestations of pericarditis, pleuritis, occasional arthralgia, and the prompt clinical response to steroid therapy usually observed. Early studies initially seem to support this view as specific circulating anti heart antibodies utilizing tanned cell hemagglutination, antiglobulin consumption, and indirect immunofluorescent techniques were identified in patients with PMIS.[16, 7] However, the specificity of this reaction could be questioned by the discovery of circulating anti heart antibodies in patients recovered from uncomplicated myocardial infarction without PMIS.[17, 4] Other studies revealed that circulating anti heart antibodies were found in approximately 50 per cent of patients following myocardial infarction[1] and tended to be present in lower titers and less persistent than PMIS. Although positive anti heart antibodies appeared either before or during development of clinical symptoms of the PMIS, and could become negative in association with clinical recovery or during clinically quiescent intervals, it was appreciated that the observed autoantibodies could represent an innocuous secondary response to tissue injury or inflammation.

As immunologic investigative methods evolved, circulating humoral immune mechanisms in PMIS have become better clarified. Circulating autoantibodies in PMIS are multiple, being directed to insoluble antigens at the sarcolemmal subsarcolemmal position of the myofibril[20] as well as to soluble antigens in saline extracts of heart. These autoantibodies present in serum and more recently detected in pericardial fluid[2] are specific for heart and skeletal muscle and have been found in association with thyroid cytoplasmic and gastric parietal cell antibodies.[2] Immunoglobulin studies of PMIS patients utilizing radial immunodiffusion and electrophoresis are scant, being reported as normal in two patients[3, 2] and an elevation of alpha 2 globulin with absence of IgA in one patient.[21] The reports of Kossowsky, Kim, and Tobin[2] and Lawrence and Wright[1] are the only described studies in the literature of cellular immunity in PMIS. Kossowsky, Kim, and Tobin's[2] studies were conducted on a patient receiving 6-mercaptopurine antimetabolite therapy and demonstrated remission of clinical symptoms when inflammatory competence (as assessed by the skin window technique of Rebuck and Crowley[14]) and delayed hypersensitivity (as indicated by 2,4-dinitrofluorobenzene[2]) were both impaired. The authors speculated that the pathogenesis of PMIS could be related to a delayed hypersensitivity reaction with injured cardiac tissue acting as the provoking antigen, and suggested that response to therapy in PMIS was mediated by an effect on nonhumoral immune or inflammatory mechanisms. Lawrence and Wright[1] could not detect a delayed hypersensitivity reaction to pericardial fluid antigen obtained from a patient with active PMIS as assessed by morphologic and tritiated thymidine incorporation lymphocyte transformation studies.

Studies conducted on our patient during remission, exacerbation of PMIS, and convalescence on steroid therapy extend these observations in a sequential manner. Assessment of humoral immunity revealed circulating anti heart autoantibody to whole heart muscle and sarcolemma during the exacerbation of PMIS and a decrease of this autoantibody with recovery. Cellular immune mechanisms, as evidenced by a positive mumps skin test, showed effective delayed hypersensitivity. In addition, the absolute lymphocyte count, percentage of lymphocytes containing surface IgG immunoglobulin (B cells), and tritiated thymidine uptake lymphocyte transformation to maximal phytohemagglutinin and pokeweed stimulation were normal during remission. Exacerbation of PMIS revealed a rise in absolute small lymphocyte count and an increase in the proportion and number of B cells. These changes returned toward normal with steroid therapy. Depressed lymphocyte transformation with recovery was presumably related to steroid therapy and returned to normal at subclinical levels of steroid therapy.

Therefore, existing data obtained during remission of PMIS seem to indicate that humoral and cellular immune mechanisms appear to be normal. Exacerbation of the syndrome results in circulating humoral immune abnormalities of

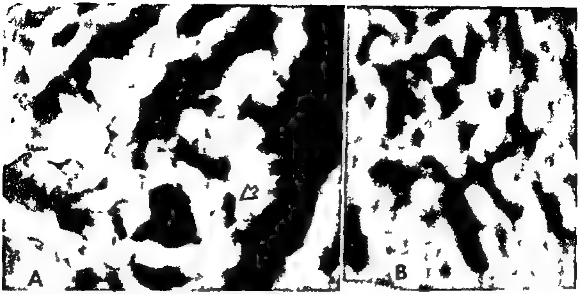

Fig 3 A and B Whole heart muscle A Sarcolemma and subsarcolemmal fluorescence with patient s serum B No fluorescence with control serum

Table III Viral studies

Study	*2/21*	*2/27*	*3/6*	*3/16*	*3/23*
Cytomegalovirus throat culture	NG	NG	NG		
Cytomegalovirus urine culture	NG	NG	NG		
Coxsackie throat culture	NG	NG	NG		
Coxsackie rectal culture	NG	NG	NG		
Coxsackie urine culture	NG	NG	NG		
Complement fixation titers					
Mycoplasma	1 16	1 16	1 16		
Adenovirus virus	1 8	1 8	1 8		
Influenza A virus	1 8	1 8	1 8		
Influenza B virus	1 16	1 16	1 16		
Mumps virus	1 16	1 16	1 32	1 16	1 16
Herpes virus	1 16	1 16			1 16
Varicella zoster virus	1 8	1 8			1 8
Cytomegalovirus	1 8	1 8			1 8
Neutralizing antibody titers					
Coxsackie B virus	1 32		1 32	1 32	1 16
Coxsackie B virus	1 256		1 256	1 256	1 256
Coxsackie B virus	1 128		1 256	1 256	1 256
Coxsackie B virus	1 32		1 64	1 32	1 32
Cytomegalovirus	1 8	1 8			1 8
Herpes virus	1 1024	1 1024			1 1024

NG = no growth

lymphocyte count with an increase in the proportion of lymphocytes containing surface IgG immunoglobulin (B cells) Lymphocyte transformation to both pokeweed and phytohemagglutinin remained normal Humoral and cellular immunologic studies were repeated during convalescence (March 6, 1973) and following remission of the PMIS (April 13, 1973) as indicated in Tables I and II

Viral studies (Table III) included cultures of throat, rectal and urine secretions obtained during the acute exacerbation of PMIS and uniformly showed no growth In addition acute and convalescent serum for complement fixation and neutralizing antibody titers revealed no acute infection Evidence of a recent herpes virus infection was present, but seemed unrelated to the present illness

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autoantibodies to heart muscle and to other tissues In addition, cellular immune abnormalities of an increased absolute lymphocyte count and increased proportion and number of "B" cells are present Remission of PMIS coincides with a decrease of circulating autoantibodies and restoration of a normal lymphocyte population During remission, evidence of impairment of cellular mechanisms may be present if steroid or antimetabolite therapy is being given To date there is little evidence that these observations have significance as causative factors in PMIS Abnormalities observed could simply represent an innocuous secondary response of a normal immune system Thus, the concept that PMIS is caused by an abnormal immune system has not been proved The recent appreciation of the early onset of PMIS in patients who had no prior overt evidence of heart disease also does not support the concept of the latent period of autoimmune disorders [6, 27] Nevertheless the clinical syndrome with its "rheumatoid like" features of polyserositis, waxing and waning natural history laboratory evidence of inflammation, and observed abnormalities of humoral and cellular immunity during exacerbations remains most closely analogous in medicine to that group of diseases designated as rheumatoid or autoimmune disorders

Viral etiology of PMIS was initially considered in the early case report of Faure and Cazeilles[28] who suggested that the idiopathic recurrent pericarditis associated with myocardial infarction might be of viral etiology facilitated by recent cardiac damage More recently, Burch and Colcolough[3] have revived interest in this possibility, and called attention to studies of experimental animals and man[29, 30] which show that some viruses are capable of infecting all tissues of the heart These viruses can remain dormant for long periods of time to be activated later by manual or chemical injury They postulated that cardiac surgery and myocardial infarction could provide the stimulus for establishment or reactivation of a latent or dormant viral infection leading to the postcardiotomy and postmyocardial infarction syndromes With the present knowledge of the potential of cardiotrophic viruses, most notably, coxsackie strains[14], as well as the appreciation that viruses can exist dormant for months or years, later giving rise to clinical syndromes (e g , herpes labialis and herpes zoster), this suggestion must be considered a credible possibility

Soloff's[17] and Degeorges, Passa, and Vann s[31] case reports of "negative viral studies" were the only reported viral data during PMIS discovered in the author's review of literature

During exacerbation and convalescence viral studies were conducted on our patient Coxsackie and cytomegaloviral cultures were negative Complement fixation titers to mycoplasma, adenovirus, influenza A, influenza B, mumps, herpes varicella zoster, and cytomegalovirus were normal Neutralizing antibody titers to coxsackie cytomegalo and herpes virus were negative Although our studies have been unrevealing it seems appropriate to obtain cultures paired acute and convalescent complement fixation and neutralizing antibody titers on serum pericardial, and pleural specimens to a variety of cardiotrophic viruses during PMIS to help clarify this possible etiology

Other possible etiologic factors proposed of a reactivated rheumatic process, trauma and foreign body reaction have not been investigated or supported authoritatively to date Thus, the etiology of PMIS remains unknown

Summary

A case of PMIS with immunologic and viral studies obtained prior, during and after a typical exacerbation are reported Immunologic studies indicated the presence of humoral antiheart autoantibodies, and an increase in the number and proportion of lymphocytes containing surface IgG immunoglobulin during acute activity Viral studies were negative Previously reported immunologic and viral data, as well as etiology and pathogenesis of PMIS are discussed

The authors gratefully acknowledge the assistance of Dr Mary F Lipscomb in the immunologic investigations

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Fig 1 Chest x ray of the right sided aortic arch. Upper arrow impression on tracheal air column Lower arrow descending aorta to right of sternum Note pleural thickening at right costophrenic angle

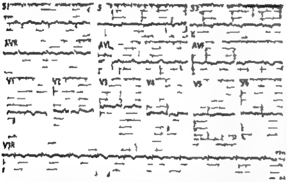

Fig 2 A. Preoperative electrocardiogram Tendency toward right axis deviation (q 90 degrees) rSr in right precordial leads abnormal T waves in Leads II III aV_F and right precordial leads, and ectopic atrial focus

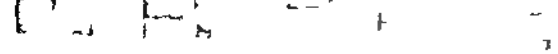

Fig 2 B Postoperative electrocardiogram Axis is q 60 degrees and T waves upright in Leads II III and aV_F

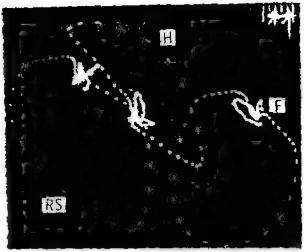

Fig 3 A Preoperative vectorcardiogram Prominent posterior and rightward forces in the horizontal plane loop and vertical axis in the frontal plane

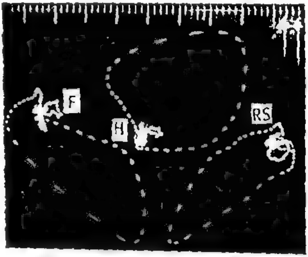

Fig 3 B Postoperative vectorcardiogram More normal terminal forces and frontal plane axis

the junction of the anterior and posterior leaflets of the tricuspid valve A 36-gram mass (Fig 9 *A*) was removed including a small portion of the endocardium with the stalk, to insure complete removal of the tumor Histologically (Figs 9 *B C* and *D*) the tumor revealed changes consistent with a myxoma

The patient was discharged after an uneventful recovery and readmitted approximately one month after surgery for re evaluation Physical examination was normal and the chest roentgenogram was unchanged The electrocardiogram (Fig 2 *B*) and the Frank vectorcardiogram (Fig 3 *B*) now revealed a mean QRS axis of q 60 degrees The right precordial rSr′ and the T wave abnormalities persisted but the T waves in the diaphragmatic leads were now upright The phonocardiogram and pulse tracings (Figs 4 *C* and *D*) showed no murmur a decrease of the splitting interval of the second heart sound

Diagnostic features of right ventricular myxoma

Stanley N Snyder, M D *
David C Smith M D **
Francis Y K Lau, M D, F A C C ***
A Franklin Turner, M D F A C C ****
Los Angeles and San Diego Calif

Primary intracardiac tumors are uncommon, and those of ventricular origin are the least frequent The intent of this communication is to report important diagnostic features noted recently in a patient with a right ventricular myxoma and relate these findings to those previously reported in the literature

Case report

This 36-year old white woman (V B) was referred for cardiac consultation as the result of a heart murmur noted on a pre employment physical examination in June 1972 She had no cardiovascular symptoms at the time of consultation and specifically denied any shortness of breath chest pain edema cough or hemoptysis She was treated successfully with antibiotics for uncomplicated pneumonia" eight months prior to consultation On review of her hospital records a nondescript systolic cardiac murmur was noted 12 years previously At that time the peripheral pulses were normal and the remainder of the examination was not remarkable

At physical examination the patient was a healthy appearing female with a blood pressure of 104/70 in both arms and normal pulse respiration and temperature A prominent a wave was noted in the jugular venous pulse There was a mild pectus excavatum and a left parasternal lift The apical impulse was in the fourth left intercostal space at the midclavicular line The first heart sound was slightly diminished The second sound was widely split and varied slightly but physiologically with respiration The pulmonic component was accentuated and audible at the apex A Grade III/VI systolic ejection murmur was heard at the third and fourth left intercostal spaces and became more prominent with inspiration A fourth heart sound was present at the left sternal border and was unchanged with the phases of respiration

Complete blood count serum electrolytes and cardiac enzymes were normal The chest roentgenogram (Fig 1) demonstrated a right sided aortic arch and pleural thickening at the right lateral base The electrocardiogram (Fig 2 A) revealed a mean QRS axis of q 90 degrees in the frontal plane and a P wave axis with leftward and superior orientation There was an rSr in Lead V and S waves in the lateral precordial leads T wave abnormalities were noted inferiorly and over the right precordium The Frank lead vectorcardiogram (Fig 3 A) demonstrated rather prominent posterior and rightward terminal forces Right ventricular hypertrophy was suggested on both the electrocardiogram and vectorcardiogram The phonocardiogram and pulse tracings (Figs 4 A and 4 B) demonstrated a systolic murmur wide splitting of the second heart sound with slight respiratory variation and a prominent a wave in the venous pulse tracing A radioisotope pulmonary perfusion scan disclosed right upper and lower lobe filling defects A 48 hour cardiac scan (Fig 5 A) utilizing 5 mCi of Ga citrate showed heavy gallium accumulation in the area of the mediastinum in the region of the sternum and extending to the left and cephalad corresponding to the location of the main pulmonary artery as demonstrated by the superimposed outline of the cardiomediastinum by a chest roentgenogram done at the same time

Preoperative cardiac catheterization (Table I and Fig 6) demonstrated a right ventricular pressure of 92/8 and a pulmonary artery pressure of 35/14 Cineangiocardiographic studies (Figs 7 A and 7 B) demonstrated a large mobile lobulated filling defect in the right ventricle extending through the pulmonary valve during systole The selective pulmonary angiogram (Fig 8 A) showed absence of some vascular branches in the right upper lobe and to a lesser degree in the right lower lobe

At surgery the right atrium left atrium and right ventricle were enlarged The left ventricle appeared normal in size There was a systolic thrill in the right ventricular outflow tract extending into the pulmonary artery The right ventricle was opened transversely revealing a gelatinous irregular mass filling much of the right ventricle and outflow tract It was attached by a narrow stalk to the right ventricular wall at

From the Los Angeles County University of Southern California Medical Center Los Angeles and the United States Naval Hospital San Diego

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Reprint requests to Dr Stanley N Snyder 9209 Colima Rd Whittier Calif 9060,

* Cardiology Fellow LAC USC Medical Center Los Angeles Calif

** Cardiologist Lieutenant Commander MC USNR United States Naval Hospital San Diego Calif

*** Professor of Medicine and Radiology LAC USC Medical Center Los Angeles Calif

**** Professor of Radiology and Medicine LAC USC Medical Center Los Angeles Calif

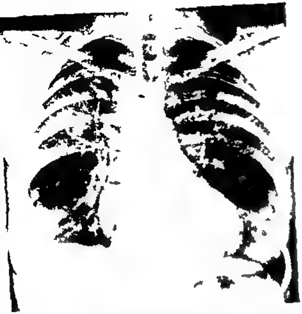


Fig 1 Chest x ray of the right sided aortic arch Upper arrow impression on tracheal air column Lower arrow descending aorta to right of sternum Note pl ural thickening at right costophrenic angle

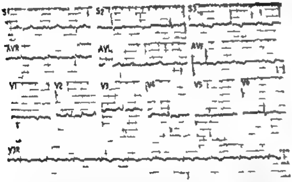
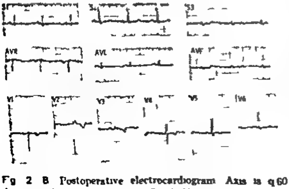


Fig 2 A. Preoperative electrocardiogram Tendency toward right axis deviation (q 90 degrees) rSr′ in right precordial leads abnormal T waves in Leads II III aV_F, and right precordial leads, and ectopic atrial focus



Fg 2 B Postoperative electrocardiogram Axis is q 60 degrees and T waves upright in Leads II III and aV_F

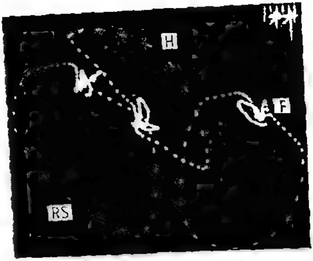
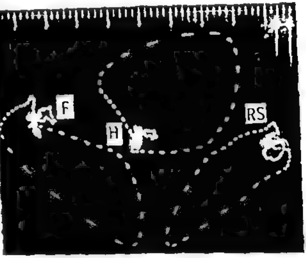


Fig 3 A Preoperative vectorcardiogram. Prominent posterior and rightward forces in the horizontal plane loop and vertical axis in the frontal plane



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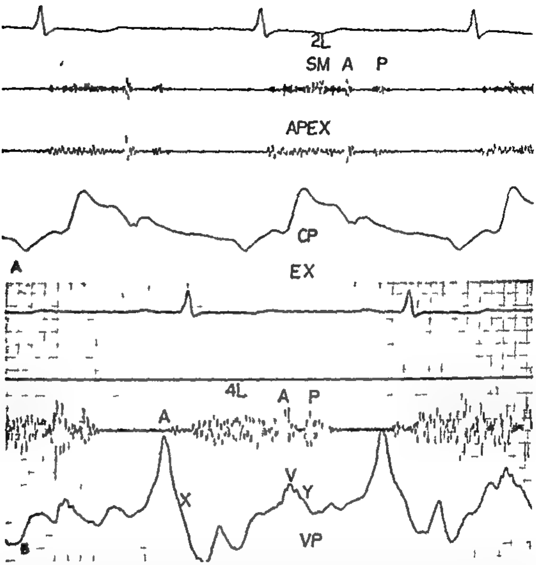

Fig 4 A and B Preoperative phonocardiogram and pulse tracings Long systolic murmur A_2 P interval 150 msec A wave of venous pulse in upper limits of normal There appears to be an abnormal relationship between P_2 and V wave *A* Paper speed = 100 mm per second SM = systolic murmur EX = expiration and CP = carotid pulse tracing *B* Paper speed = 100 mm per second and VP = venous pulse

and a normal venous pulse tracing Cardiac catheterization (Table I) disclosed a right ventricular pressure of 35/5 with no outflow gradient The right ventricular filling defects were absent (Fig 7 *C*) The radioisotope pulmonary perfusion scan and pulmonary angiograms (Fig 8 *B*) were unchanged Six months postoperatively a 48 hour cardiac scan (Fig 5 *B*) again using 5 mCi Ga citrate revealed less gallium uptake in the area where the tumor had been

Review of 16 cases

This is the sixteenth case of right ventricular myxoma in our review of the world literature (Table II) Except for Catton Guntheroth and Reichenbach s case the patients ages ranged from 16 to 56 most being young adults at the time of diagnosis There was slight predominance of females Symptoms or signs antedated diagnosis by as much as 14 years Only two patients were without complaint Fever shortness of breath chest pain cyanosis syncope seizures and sudden death have been described In two cases pain was exertional and exertional syncope was noted in another patient

In one instance episodes of positional palpitation were caused by ventricular tachycardia The most common physical finding (14 out of 16 patients) was a Grade III to IV/VI systolic murmur along the left sternal border and of maximal intensity in the second or third intercostal space Some authors described changes in intensity or location of the murmur from time to time In one instance these changes occurred after cardiac catheterization Some were associated with a palpable thrill and a peculiar feeling of movement or a worm like thrill has been described A right ventricular lift was noted occasionally In our case and in one other the pulmonic component of the second sound was separated from the aortic component by an interval of 100 to 130 msec In most reports no information was available with regard to the second heart sound To and fro scratches and clicks simulating pericarditis have been described with right ventricular myxoma and a diastolic murmur was noted in one patient Several patients had elevated jugular venous pressure and prominent a waves Two patients presented with fever and three patients were noted to be cyanotic

Electrocardiographic abnormalities included right axis devi

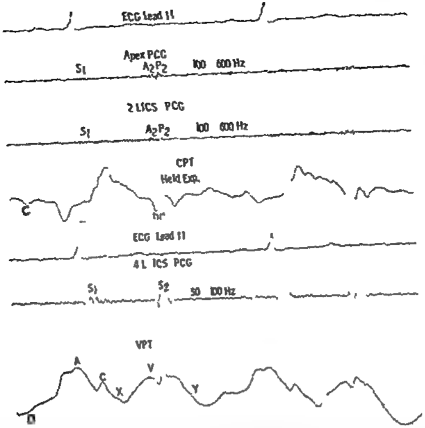

Fig 4 C and D Postoperative phonocardiogram and pulse tracings Murmur is now absent A P relationship is normal A wave is less prominent and there is restoration of the normal relationship between P and the V wave peak C Paper speed = 100 mm per second ECG = Lead II electrocardiogram Apex PCG = phonocardiogram apex 2 LICS PCG = phonocardiogram second left interspace parasternal line CPT = carotid pulse tracing and DC = dicrotic notch D Paper speed = 100 mm per second ECG = Lead II electrocardiogram 4 LICS PCG = phonocardiogram fourth left interspace parasternal line and VPT = venous pulse tracing

ation (eight patients) the so called incomplete right bundle branch block pattern (five patients) complete right bundle branch block (three patients) right ventricular hypertrophy (five patients) and right atrial enlargement (two patients) Abnormal T waves in the inferior and/or right precordial leads were also noted (six patients) Three chest roentgenograms were normal four disclosed enlargement of the main pulmonary artery and three were virtually diagnostic of intracardiac tumor by the presence of calcification in the area of the right ventricular outflow tract Right ventricular enlargement was noted in two patients Decreased pulmonary vascularity enlarged main pulmonary artery gross cardiomegaly and right atrial enlargement were each noted in one case Increased pulmonary vascularity was present in a patient who had in addition an atrial-septal defect Our case was normal roentgenographically except for a right sided aortic arch and right costophrenic pleural thickening

At cardiac catheterization significant right ventricle to-pulmonary artery gradients were present in most patients Occasionally as in our patient an infundibular chamber was simulated The right ventricular pressure was over 60 mm Hg in the majority of patients, with a range of 44 to 140 mm Hg Cineangiocardiography was diagnostic with the demonstration of filling defects in the right ventricle or its outflow tract Diagnosis prior to surgery was not made in the absence of right ventricular calcification or cineangiocardiography In one of these cases a coincidental atrial septal defect was correctly diagnosed but the tumor went undetected. Eleven out of thirteen patients operated upon survived, one patient having residual symptoms. In two patients diagnosis was made at autopsy

The tumors were attached by single or multiple pedicles most frequently to the right ventricular septum or free wall but other sites of origin included the conus the chordae the pulmonary artery and also the ventricular surface of the tricuspid or pulmonic valves The tumors were described pathologically as myxoma tissue alone except for four instances in which additional tissue origins were noted

Discussion

Fourteen out of sixteen patients had murmurs at the left sternal border that suggested right ventricular outflow obstruction The physical findings associated with right ventricular myxoma strongly resemble those of pulmonic valvular

Fig 5 A Preoperative cardiac scan anterior and posterior Heavy concentration of gallium in the mid chest area extending leftward and cephalad from right ventricle toward the main pulmonary artery

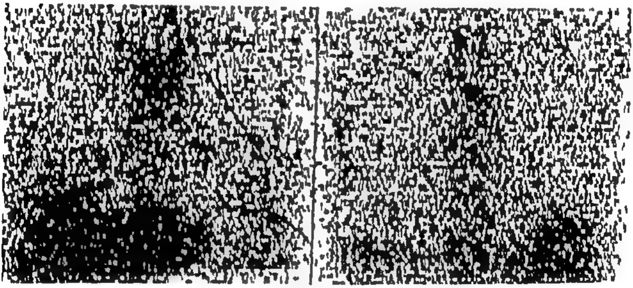

Fig 5 B Postoperative cardiac scan anterior and posterior Considerable decrease in concentration of gallium in the mid chest region and the extension toward the pulmonary artery is now absent

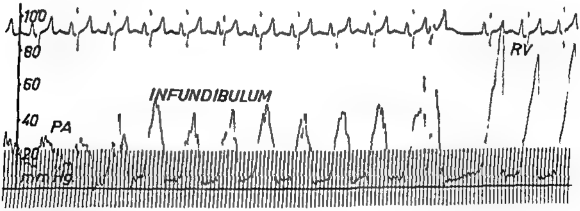

Fig 6 Preoperative pressure tracing During cardiac catheterization with pullback from main pulmonary artery to infundibulum to right ventricle demonstrating pressure gradients

Fig 7 A Preoperative cineangiography of right ventricle and outflow tract Large mobile filling defect occupying portions of the right ventricle and extending through the pulmonary valve (during systole)

Fig 7 C Postoperative cineangiogram of right ventricle and outflow tract Absence of the previously described filling defect

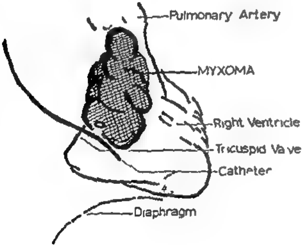

Fig 7 B Diagrammatic illustration of filling defect noted in Fig. 7 A

or infundibular stenosis. The dramatic history of effort syncope can occur in all three entities With regard to age of onset Catton Guntheroth and Reichenbach's two month old patient suggests that age of onset of symptoms and signs may not be helpful

When present a widely split and accentuated pulmonic component of the second heart sound noted by Sakakibara and co workers [1] and present authors may be the best differentiating physical finding accompanying the systolic murmur With pulmonic valvular or infundibular stenosis wide splitting of the second sound is expected but the pulmonic component is not accentuated The delayed and accentuated pulmonic component may be due to prolonged right ventricular obstruction or right bundle branch block The pulmonic valve closure may be delayed due to prolapse of the tumor through the pulmonic valve The accentuation of the pulmonic component may have its origin as a result of tumor pulmonary emboli and secondary pulmonary hypertension

An ejection click was noted in only one of the cases of right ventricular myxoma [1] and when present usually suggests pulmonic valvular stenosis rather than myxoma

The flow murmurs associated with atrial septal defect ventricular septal defect and idiopathic dilation of the pulmonary artery may have similar physical findings as a right ventricular myxoma Patients with atrial septal defects usually exhibit fixed second sound splitting seldom greater than 80 msec and have chest roentgenograms showing increased flow The ven

Fig 8 A Preoperative pulmonary angiogram Filling defect in right upper lobe of lung considerable peripheral disorganization particularly in the right lower lobe and pleural thickening in the right costophrenic angle

Fig 8 B Pulmonary angiogram approximately five weeks postoperative Essentially unchanged from preoperative study with failure to demonstrate improved flow to the right upper lobe of the lung

Table I Cardiac catheterization

Position	Preoperative (6/72)			Postoperative (8/72)		
	Pressure		O_2 Saturation	Pressure		O_2 Saturation
Right atrium	$\overline{7}$		6[illegible]	$\overline{10}$		[illegible]
Right ventricle		92/8	60		35/5	55
Right ventricular infundibulum		58/7	—		35/5	—
Pulmonary artery	$\overline{20}$	35/14	6[illegible]	$\overline{20}$	35/10	54
Left ventricle		104/7	94		—	—
Aorta	$\overline{77}$	104/62	93	$\overline{80}$	115/65	96
Cardiac output (Fick)	3 51 L /min			3 57 L /min		
Cardiac index	2 17 L /min /M			2 20 L /min /M		

— After angiogram

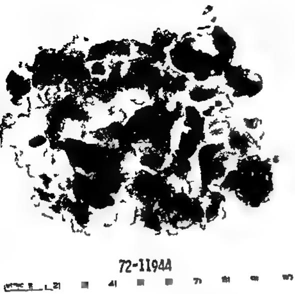

Fig 9 A. Macroscopic tumor tissue

Fig 9 B and C Low power microscope tumor tissue

tricular septal defects usually have similar chest roentgenographic findings to atrial septal defects and usually electrocardiographic evidence of left ventricular hypertrophy Calcification in the region of the right ventricular outflow tract that

Fig 9 D High power microscope tumor tissue

moves with the cardiac cycle is virtually diagnostic of an intracavitary tumor ^{67}Ga scanning helped to localize and diagnose the obstructive right ventricular problem Follow up scanning should be delayed until two to six months after surgery because healing tissue may concentrate gallium similarly to tumor tissue

The presence of a pressure gradient across the right ventricular outflow tract and angiographic identification verifies the diagnosis of right ventricular tumor The management of this lesion should be early surgery to avoid the possibility of sudden death. The review of the literature reveals that 12 out of 13 patients including ours survived their surgery Prognosis following surgical removal of the tumor is excellent with no recurrences having been noted in the previously described cases Other tumors of the right ventricle such as sarcomas rhabdomyomas metastases and endometriosis may clinically simulate myxomas but do not have as good a surgical prognosis

Summary

The clinical diagnostic features of right ventricular myxoma are described in a recent patient

Table II

Author(s)	Year reported	Age	Sex	RV to PA gradient (mm Hg)	RV angiogram	Method of diagnosis	Surgery	Result
1 Kishimoto and Sakaibori	1959	27	F	Unknown	Not done	Autopsy	No	Died
2 Michaud et al	1960	17	M	35	Filling defect	Catheterization	Yes	L & W
3 MacRae and Galea	1961	21	M	Unknown	Not done	Autopsy	No	Died
4 Ernst et al	1962	56	F	51	Not done	Chest roentgenogram and catheterization	Yes	L & W
5 Dong et al	1962	55	F	77	Filling defect	Catheterization	Yes	Neurological deficit
6 Gottsegen et al	1963	16	M	92	Not done	Surgery	Yes	Died
7 Catton et al	1963	1/6	M	Unknown (RV = 140)	Deformed valve	Surgery	Yes	Died
8 Doohen et al	1964	26	M	40	Filling defect	Catheterization	Yes	L & W
9 Crummy and Hipona	1964	21	F	61	Filling defect	Catheterization	Yes	L & W
10 Wada et al	1965	16	M	60	Filling defect	Catheterization	Yes	L & W
11 Sakakibara et al	1965	18	F	12	Filling defect	Catheterization	Yes	L & W
12 Byron and Thompson	1966	39	F	18	Not done	Surgery	Yes	L & W
13 Morrow et al	1966	21	M	48	Filling defect	Catheterization	Yes	L & W
14 Hubbard and Neil	1971	39	F	Unknown	Not done	Chest roentgenogram	No	Died
15 Warembourg et al	1971	16	F	8 (isoproterenol)	Filling defect	Catheterization	Yes	L & W
16 Present case	1973	36	F	57	Filling defect	Catheterization	Yes	L & W

F = female M = male L & W = living and well PA = pulmonary artery RV = right ventricle

and related to the 15 cases previously reported The presence of a pulmonic systolic ejection murmur with a delayed (120 to 140 msec) and accentuated pulmonic second sound or calcification in the region of the right ventricular outflow tract should suggest this lesion Cardiac catheterization with angiocardiography is diagnostic ^{67}Ga scanning may assist in the diagnosis and follow up after surgical removal of the myxoma Early surgical removal will avoid the possibility of sudden death

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Clinical pathologic conference

Steven D Chernausek B A
David S Swan M D
James H Moller M D
Zeev Vlodaver M D
Jesse E Edwards M D
St Paul and Minneapolis Minn.

STEVEN D CHERNAUSEK B A * The patient was a 3-day old girl who was born following a term pregnancy and normal delivery. The birth weight was 3 040 grams. The Apgar score at 1 minute was 10 and the infant appeared healthy and normal. At 1 day of age however cyanosis and a cardiac murmur were noted. The patient was transferred for evaluation and management.

Physical examination revealed a cyanotic tachypneic infant. Simultaneous flush blood pressures in the arm and leg were 36 mm Hg. The pulse rate was 130 per minute and the respiratory rate was 100 per minute. The thorax was symmetrical. Subcostal and intercostal retraction was present. The lungs were clear to auscultation. The first heart sound was loud and the second, single. A Grade III/VI systolic murmur was heard at the base but not over the back. The edge of the liver was palpable 3 cm below the right costal margin.

The blood counts and levels of serum electrolytes obtained upon admission were within normal limits. Arterial P_{O_2} while breathing room air was 54 mm Hg.

A thoracic roentgenogram and electrocardiogram (ECG) were obtained. Dr Swan would you interpret these studies?

DAVID S SWAN M D The thoracic roentgenogram (Fig 1) demonstrated cardiomegaly and signs of increased pulmonary blood flow which in the presence of cyanosis suggests an admixture lesion. Furthermore the aortic arch was probably right sided which together with the other roentgenographic features would heavily favor a diagnosis of persistent truncus arteriosus. The ECG showed sinus tachycardia and a QRS axis of 90 degrees (Fig 2). Signs of right atrial enlargement were also present. The striking finding related to the QRS complex and ST T wave changes. The precordial leads show a bizarre QRS configuration in Lead V_4 and a qR pattern in Lead V_6. These are compatible with an anterolateral myocardial infarction. ST segment alterations were also present. We felt that the ECG indicated myocardial damage and that it was a very unusual tracing for our presumed diagnosis of truncus arteriosus.

MR. CHERNAUSEK Digoxin therapy was initiated but the infant s status failed to improve. Cardiac catheterization was performed. This study revealed a 50 per cent left to right shunt at the atrial level. Right ventricular systolic pressure was 90/0 15 mm Hg. Right ventriculography revealed a ventricular septal defect and simultaneous opacification both of the aorta and the pulmonary arterial system (Fig 3 *A*). Separate aortic and pulmonary valves could not be clearly visualized. The right ventricle emptied slowly contrast material remaining in the ventricle for at least [illegible] seconds. There was a right aortic arch. The catheter could not be advanced into either the left ventricle or aorta. When severe bradycardia developed while attempting to pass the catheter to the latter site the study was terminated.

On review of the films a definite diagnosis could not be made between the origins of both great vessels from the right ventricle and truncus arteriosus. In either case myocardial function was depressed.

During the second day of life the infant s

From the Department of Pathology United Hospitals-Miller Division St Paul and the Departments of Pediatrics and Pathology University of Minnesota, Minneapolis Minn

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Reprint requests Jesse E Edwards M D Department of Pathology United Hospitals-Miller Division [illegible] College A[illegible] St Paul Minn 55102.

*Medical Student, University of Minnesota

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Fig 1 Thoracic roentgenogram in frontal view

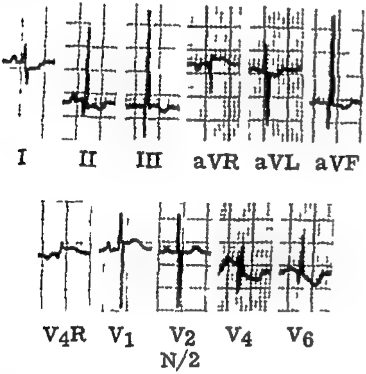

Fig 2 Electrocardiogram

condition became worse Signs of congestive cardiac failure and intravascular coagulation developed An exchange transfusion was performed As the patient s condition continued to deteriorate respiratory treatment was begun

The following day further invasive studies were done Dr Swan, will you describe the results of these?

Dr Swan We felt that an aortogram would clearly differentiate between origin of both great vessels from the right ventricle and truncus arteriosus Therefore a retrograde aortogram was performed from the left brachial artery This study revealed an aberrant left subclavian artery originating from the descending aorta in the presence of a right aortic arch Realizing that it would be extremely difficult to pass a catheter into the ascending aorta from this site, the aberrant left subclavian artery, we terminated this part of the study Then, through the right brachial artery, a catheter was advanced to the ascending aorta and an aortogram performed (Fig 3, *B*) A single arterial vessel arising from the heart was present and, from this, the pulmonary arteries arose These features established the diagnosis of persistent truncus arteriosus The truncal valve appeared thickened and domed but there was no insufficiency of this valve The right coronary artery was visualized but we could not visualize the left coronary artery We had no explanation for the failure to visualize the left coronary artery but certainly this finding correlated with the ECG pattern of a myocardial infarction and the angiographic evidence of depressed myocardial function

Mr Chernausek Thank you Dr Swan The infant remained in a state of congestive cardiac failure despite therapy with a digitalis preparation diuretics and a respirator There was progressive depletion of clotting factors Death occurred 2 hours after the aortogram on the third hospital day

Dr Moller, would you discuss the differential diagnosis?

James H Moller M D This patient presented rather unique diagnostic problems The child showed cyanosis and increased pulmonary vascular markings which led us to the diseases grouped as admixture lesions, namely, conditions such as complete transposition of the great vessels, persistent truncus arteriosus total anomalous pulmonary venous connection and single ventricle The presence of a right aortic arch was an important finding which led us to favor truncus arteriosus

Classically truncus arteriosus does not lead to congestive cardiac failure in the newborn period In this condition the development of cardiac failure is dependent upon volume overloading of the left ventricle In the newborn period pulmonary vascular resistance is markedly elevated and approaches the level of systemic vascular resistance As a result the volume of pulmonary blood flow is not much greater than systemic blood flow With maturation of the pulmonary vascular bed and corresponding fall in pulmonary vascular resistance, flow increases But this evolution requires several wee

Fig 3 *A* Right ventriculogram in lateral view *B* "Aortogram in frontal view

months to occur so that cardiac failure commonly does not occur until about 6 weeks to 3 months after birth

Important diagnostic clues in this patient were the presence of cardiac failure in the neonatal period and the striking ECG pattern A pattern of anterolateral myocardial infarction in the ECG of a newborn infant is rare particularly when a coexistent shunt lesion is present There are several conditions which might cause myocardial infarction in a newborn infant that can be considered related either to isolated coronary arterial problems or to changes occurring secondary to other cardiac anomalies

Anomalous origin of the left coronary artery is the classic example of a coronary arterial anomaly leading to a myocardial infarction In this anomaly myocardial infarction does not to our knowledge occur in the neonatal period

Recently the anomalous course of a coronary arterial vessel has been related to sudden death but not in a neonate Thrombocytosis and elevated serum calcium have been associated with myocardial necrosis in the neonatal period but laboratory studies in our patient excluded these possibilities

Myocardial damage may occur with other congenital cardiac anomalies typically those involving the aortic valve or supravalvular area Congenital aortic stenosis in neonates is associated with subendocardial fibrosis and occasionally leads to a pattern of myocardial infarction Supravalvular aortic stenosis may be associated with myocardial damage because of three factors (1) elevated myocardial oxygen requirement (2) elevated pressure on the coronary arteries leading to atherosclerosis and (3) encroachment on coronary ostia by either the supravalvular tissue or the thickened aortic valvular tissue

None of these conditions involving the coronary arteries occurs with truncus arteriosus that we are aware of In our patient the left coronary artery did not opacify following injection of contrast material into the aortic root It is possible that the left coronary artery was hypoplastic or that its ostium was occluded in the process which had thickened the truncal valve

By some mechanism flow through the left coronary arterial system was impaired yielding the pattern of myocardial infarction and the poor contractility of the left ventricle The latter in turn in our view accounted for the unusual finding of cardiac failure in a neonate with truncus arteriosus

My diagnoses are persistent truncus arteriosus and some obstructive lesion of the left coronary artery the latter accounting for myocardial infarction

MR. CHERNAUSEK Thank you Dr Moller Dr Vlodaver would you summarize the autopsy findings?

ZEEV VLODAVER, M D The heart and lungs weighed 62 grams Examination of the heart showed a single vessel or truncus arteriosus arising from both ventricles immediately above a ventricular septal defect It supplied the coro

Fig 1 Thoracic roentgenogram in frontal view

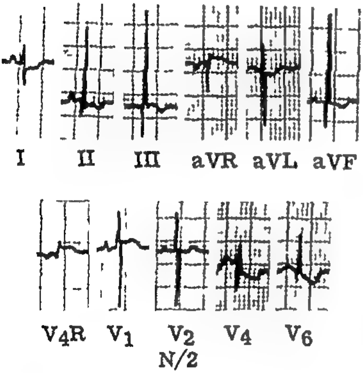

Fig 2 Electrocardiogram

condition became worse. Signs of congestive cardiac failure and intravascular coagulation developed. An exchange transfusion was performed. As the patient's condition continued to deteriorate, respiratory treatment was begun.

The following day, further invasive studies were done. Dr Swan, will you describe the results of these?

DR SWAN: We felt that an aortogram would clearly differentiate between origin of both great vessels from the right ventricle and truncus arteriosus. Therefore, a retrograde aortogram was performed from the left brachial artery. This study revealed an aberrant left subclavian artery originating from the descending aorta in the presence of a right aortic arch. Realizing that it would be extremely difficult to pass a catheter into the ascending aorta from this site, the aberrant left subclavian artery, we terminated this part of the study. Then, through the right brachial artery, a catheter was advanced to the ascending aorta and an aortogram performed (Fig 3, *B*). A single arterial vessel arising from the heart was present and from this, the pulmonary arteries arose. These features established the diagnosis of persistent truncus arteriosus. The truncal valve appeared thickened and domed but there was no insufficiency of this valve. The right coronary artery was visualized but we could not visualize the left coronary artery. We had no explanation for the failure to visualize the left coronary artery but certainly this finding correlated with the ECG pattern of a myocardial infarction and the angiographic evidence of depressed myocardial function.

MR. CHERNAUSEK: Thank you, Dr Swan. The infant remained in a state of congestive cardiac failure despite therapy with a digitalis preparation, diuretics, and a respirator. There was progressive depletion of clotting factors. Death occurred 2 hours after the aortogram on the third hospital day.

Dr Moller, would you discuss the differential diagnosis?

JAMES H MOLLER, M D: This patient presented rather unique diagnostic problems. The child showed cyanosis and increased pulmonary vascular markings which led us to the diseases grouped as admixture lesions, namely, conditions such as complete transposition of the great vessels, persistent truncus arteriosus, total anomalous pulmonary venous connection, and single ventricle. The presence of a right aortic arch was an important finding which led us to favor truncus arteriosus.

Classically, truncus arteriosus does not lead to congestive cardiac failure in the newborn period. In this condition, the development of cardiac failure is dependent upon volume overloading of the left ventricle. In the newborn period, pulmonary vascular resistance is markedly elevated and approaches the level of systemic vascular resistance. As a result, the volume of pulmonary blood flow is not much greater than systemic blood flow. With maturation of the pulmonary vascular bed and corresponding fall in pulmonary vascular resistance, flow increases. But this evolution requires several weeks or

cusp being thickened and dysplastic Two coronary arteries arose from the truncus and coursed normally The ostium of the right coronary artery was of normal caliber and was highly positioned The left coronary ostium was hypoplastic stenotic and partially covered by the left dysplastic aortic cusp

The myocardium showed [illegible] pale discoloration in the apical half of the ventricular septum representing acute infarction (Fig 4 *A*) The mitral and tricuspid valves were normal The right ventricular wall measured 4 mm in thickness and the left [illegible] mm The atrial septum showed a small defect on the basis of a short valve of the foramen ovale The lungs were hemorrhagic

The most significant histologic findings involved the myocardium the wall of the truncus arteriosus and the coronary arterial system

Serial sections taken through the truncal wall and the stenotic ostium of the left coronary artery revealed a mosaic configuration to the elements of the truncal wall (Fig 4 *B*) The left coronary artery as it passed through this wall was strikingly narrow but did not show intrinsic abnormality (Fig 4 *C*) Beyond the truncal wall the left coronary arterial system was of normal structure as was the right coronary artery

The truncal valve was dysplastic containing relatively large amounts of cellular young connective tissue In one of the sections the free edge of the left truncal cusp was attached to the truncal wall (Fig 4 *D*)

The discolored area of the ventricular septum noted grossly showed a picture of myocardial infarction characterized by eosinophilia and cytoplasmic clumping of the myocardial fibers and early interstitial leukocytic infiltration The infarct was considered to be about 24 hours old (Fig 5) The remainder of the myocardium was not remarkable

MR. CHERNAUSEK Thank you Dr Vlodaver Dr Edwards would you make some closing remarks?

JESSE E EDWARDS M D The point of principal interest in the case presented is that acute myocardial infarction occurred in the neonatal period Anomalies involving the coronary arteries are relatively uncommon among all cases of congenital cardiac disease The most common anomaly of significance is that in which the left coronary artery arises from the pulmonary trunk

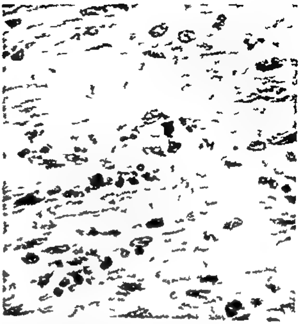

Fig 5 Photomicrograph of a section through the discolored area of the ventricular septum showing a picture of early interstitial leukocytic infiltration in acute myocardial infarction (Hematoxylin and eosin × 450)

In the current case both coronary arteries arose from normal sites of the associated persistent truncus arteriosus

The significant feature leading to acute myocardial infarction was that the left coronary artery was stenotic at its origin The case appears to be an example of an uncommon condition which at this point in time has not generally been recognized

The condition is one of stenosis of the left coronary arterial origin in association with a peculiar mosaic orientation of the elements of the aorta or as in this case the truncus arteriosus

The mosaic pattern of the aorta is shared with classical cases of supravalvular aortic stenosis but in the case presented and in two others which Dr Vlodaver and I have observed, in each of which there was a true aorta the aortic medial lesion noted histologically was not associated with obstruction of the aorta

According to our current views the condition may be considered a variant of supravalvular aortic stenosis in which the effects upon the left coronary artery dominate

In each of the two other cases which Dr Vlodaver and I observed the mitral valve leaflets showed a scalloped effect from upward protrusion of tissue between chordal attachments Such

Fig 4 *A* Specimen of interior of right ventricle (*R V*) and the persistent truncus arteriosus (*T.A*) arising above a ventricular septal defect (*D*) The origins of the two pulmonary arteries (*P.A*) lie close together in the posterior wall of the truncus The ventricular septum shows a zone of pale discoloration (between arrows) representing acute myocardial infarction *B* Photomicrograph of truncal wall showing a disarray of elements consistent with a mosaic pattern (Elastic tissue stain × 25) *C* Photomicrograph of the wall of the truncus arteriosus at the level of the origin of the left coronary (*L C*) from it The vessel is narrow The dysplastic truncal valve (*V*) also appears in the section (Elastic tissue stain × 24) *D* A portion of the truncal valve (*V*) and the left coronary artery (*L C*) after it has left the truncus arteriosus (*T*) The dysplastic valve is adherent to the sinus wall The left coronary artery after leaving the truncus is essentially normal (Elastic tissue stain × 12.5)

nary pulmonary and systemic circulation The pulmonary arteries arose independently but close to each other from the posterior aspect of the truncus arteriosus The truncus then continued as the aorta The aortic arch was right sided From before, backward, its branches were the left common carotid, the right common carotid the right subclavian the right vertebral and an aberrant left subclavian artery It was possible to delineate three cusps of the truncal valve, each

The renal blood supply in oliguric states. When is a kidney ischemic? A fundamental in cardiology

Norman K. Hollenberg, M.D., Ph.D.
Douglass F. Adams, M.D.
Boston, Mass.

Among obstacles which stand in the way of understanding, the most pernicious, according to Sir Francis Bacon (1561-1626), the English philosopher, are those due to pitfalls intrinsic to language. Words used in everyday discourse often come to be employed indiscriminately. The term *ischemia* is a contemporary example. As generally used, the term is perhaps too familiar to physicians, conjuring up visions of tissue hypoxia and cell destruction. Indeed, a widely read textbook on pathology discussed ischemia in a chapter entitled "The dead and dying cell." According to *Taber's Medical Dictionary*, the term is derived from the Greek *ischein* (to hold back) and *aeima* (blood). On this basis *any* reduction of blood flow to a tissue represents ischemia. Clearly, such a broad use of the term destroys its utility. A definition which specifies a blood flow reduction sufficient to modify function in the region underperfused has greater utility. In that context, a reduction in perfusion influences the function of the kidney differently from a critical reduction of blood flow, for example, to skeletal muscle or the myocardium.

In such metabolically active organs as the heart, brain, postprandial intestine, and skeletal muscle during exercise, the vascular supply has primarily a "grocery and garbage function," providing oxygen and the substrates required for oxidative processes and removing metabolic waste products. In these tissues ischemia modifies function when it interferes with metabolism. The cells are truly starved, strangled, and prone to destruction unless their activity falls to a level commensurate with their blood supply. This process accounts for angina pectoris and myocardial infarction in the case of the heart and intermittent claudication and gangrene in the extremity.

In contrast, the kidney enjoys a luxurious perfusion rate: about 300 grams of renal tissue receive over 20 per cent of the cardiac output, resulting in an average flow per gram of approximately 4 ml. per minute. This level is about four times that of the heart, brain, intestine, and exercising skeletal muscle, and thus clearly exceeds the usual grocery function of the arterial supply.[1, 2] In most tissues oxygen utilization is a major determinant of blood flow. The kidney is unique in that blood flow is ultimately one of the determinants of oxygen utilization.[3] An increase in renal blood flow, to the extent that it is accompanied by an increase in the rate of glomerular filtration, results in an increase in oxygen consumption. This is because the major metabolic cost of renal function is the support of active tubular reabsorptive processes, especially those responsible for sodium handling. An increase in the rate of glomerular filtration results in an increase in the load presented to the tubule for reabsorption, and thus in an increase in the oxygen requirement.

In the last two decades it has become apparent that the renal vasculature contributes to renal function in several ways. (1) As with other vascular beds, the blood flow provides oxygen and

From the Departments of Radiology and Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass.

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Reprint requests: Dr. Norman K. Hollenberg, Peter Bent Brigham Hospital, 721 Huntington Ave., Boston, Mass. 02115.

attenuations of the mitral valve were described in classical cases of supravalvular aortic stenosis from this laboratory by Becker and associates[1] The fact that we have seen similar changes in two cases with left coronary ostial stenosis is further support of the concept that the coronary arterial disease under discussion is a dominant part of the syndrome of supravalvular aortic stenosis

Of the two other cases observed by us, one was a female infant who manifested signs of coronary disease beginning at about 3 months of age Death from congestive cardiac failure occurred at the age of 15 months Details of this case were reported by Price and associates[2]

The second case yet unreported, was a 4 year old, asymptomatic boy who died suddenly

The question yet remains for a proper designation of this entity At the moment, we favor "supravalvular aortic stenosis, *forme fruste*, with left coronary ostial stenosis"

FINAL DIAGNOSES

1 Supravalvular aortic stenosis, *forme fruste*, with left coronary ostial stenosis
2 Neonatal acute myocardial infarction
3 Persistent truncus arteriosus, type II
4 Right aortic arch with aberrant left subclavian artery
5 Atrial septal defect, small

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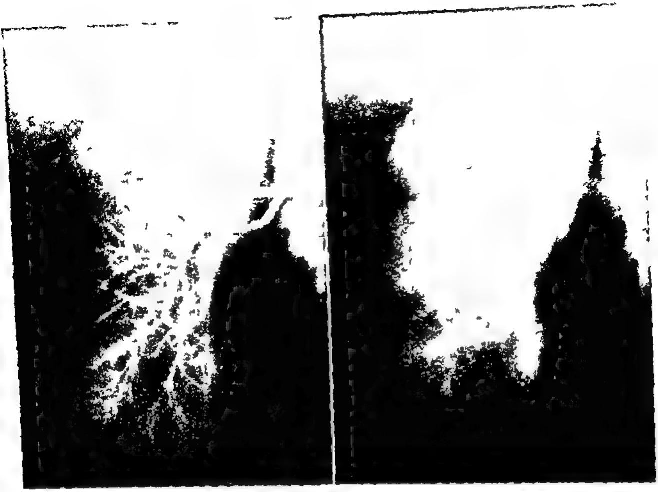

Fig. 2. Acute renal failure developed in this 53-year-old man 3 weeks after mitral valve replacement. A strong suspicion of renal embolism was entertained and consequently arteriography was performed. (*Left*) Arterial phase. The main renal artery in its large branches appears normal and shows no evidence of embolization. The intrarenal branches are spread and fill poorly toward the periphery of the kidney, which is swollen and enlarged. (*Right*) Nephrographic phase. The perfusion of the periphery of the kidney is grossly diminished, and a clear cortical medullary demarcation is absent. There is no evidence of renal venous opacification. The patient's clinical course and the histologic features of the kidney suggested acute renal failure, probably due to a nephrotoxin, colistimethate. (From Hollenberg et al. In Abrams, H. L. Angiography, ed. 2, Boston, 1971, Little, Brown & Company.)

required by this region probably accounts for the development of papillary necrosis in a number of clinically important conditions.

In view of the critical role that the renal blood supply plays in the support of renal function, it is not surprising that visualization of the renal arterial tree by arteriography has provided insight into the pathogenesis and come to play a role in the evaluation of selected patients with acute oliguric renal failure states.[3] In addition, the application of tracer techniques, specifically radioactive xenon washout, has provided an index of cortical perfusion in normal man and in patients with acute oliguric renal failure of diverse etiology.[4]

Acute organic renal arterial obstruction

The kidney is not immune from vascular catastrophes. Indeed, acute renal vascular occlusion due to renal arterial embolism, thrombosis, or dissecting aneurysm of the aorta occurs with sufficient frequency that it represents an important, potentially remediable part of the differential diagnosis of acute renal failure states. Because there is a clear-cut relationship between the duration of ischemia and the probability and

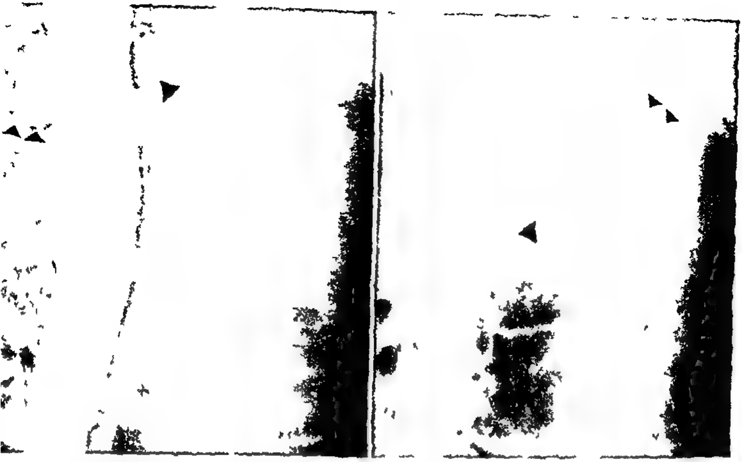

Fig 1 Renal embolism resulting in anuria This 60 year old woman had her right kidney removed 20 years earlier She developed anuria and flank pain after a paroxysm of atrial fibrillation (*Left*) Anteroposterior study 1 5 seconds after aortic injection of contrast agent The stump of the right renal artery ligated at the time of prior nephrectomy is clearly defined (double arrow) On the left there is total occlusion of the left renal artery by embolus (single arrow) Small para aortic collateral channels are visible (*Right*) Two seconds later the intrarenal vessels are filled with contrast agent via direct channels from the aorta as well as from the lumbar branches The *reconstituted renal artery (single arrow) indicates* the length of the embolic obstruction which was verified at surgery The edge of the kidney (double arrow) is now defined by *faint contrast staining indicating* the passage of contrast and therefore blood into the peripheral circulation of the kidney The kidney was viable despite 30 hours of total occlusion of the renal artery (From Hollenberg et al *In* Abrams H L Angiography ed 2 Boston 1971 Little Brown & Company)

substrate for renal metabolism but as has ... pointed out the perfusion level far exceeds ...e requirements (2) The extremely high perfu... rate in the kidney is confined to the renal ...ex, where it presents to the glomerulus large ...mes of plasma for filtration and the force ...noting filtration, glomerular capillary hy...tatic pressure Glomerular capillary pressure ... force which initiates nephron function ...ugh the creation of a plasma ultrafiltrate in ...glomerulus is among the highest in the body ...ian this hydrostatic pressure and the permea...y of the membrane are sufficient to create ...it 180 liters of ultrafiltrate per day (3) An ...tional relevant factor is that peritubular ...llary hydrostatic pressure in the cortex is ...tantially lower than in most other capillar...ies a sharp pressure drop occurs at both the preglomerular and the postglomerular arteriolar level Moreover, peritubular capillary plasma oncotic pressure is increased by the filtration of 20 per cent of the plasma water in the glomerulus Both factors enhance peritubular capillary fluid reabsorption—a phenomenon which may well have important implications for sodium handling by the kidney [4] (4) Finally, perfusion of the renal papilla at a level of about 0 2 ml per gram per minute is considerably lower than that in most active tissues This reduced flow rate facilitates the counter current mechanism and water handling by the kidney because a higher flow rate would wash out the osmolal gradient required for water reabsorption and concentration of the urine [2,3] The rather precarious blood flow

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the substrate for renal metabolism but as has been pointed out the perfusion level far exceeds these requirements (2) The extremely high perfusion rate in the kidney is confined to the renal cortex, where it presents to the glomerulus large volumes of plasma for filtration and the force promoting filtration glomerular capillary hydrostatic pressure Glomerular capillary pressure, the force which initiates nephron function through the creation of a plasma ultrafiltrate in the glomerulus, is among the highest in the body In man this hydrostatic pressure and the permeability of the membrane are sufficient to create about 180 liters of ultrafiltrate per day (3) An additional relevant factor is that peritubular capillary hydrostatic pressure in the cortex is substantially lower than in most other capillaries a sharp pressure drop occurs at both the preglomerular and the postglomerular arteriolar level Moreover peritubular capillary plasma oncotic pressure is increased by the filtration of 20 per cent of the plasma water in the glomerulus Both factors enhance peritubular capillary fluid reabsorption—a phenomenon which may well have important implications for sodium handling by the kidney [4] (4) Finally, perfusion of the renal papilla at a level of about 0 2 ml per gram per minute is considerably lower than that in most active tissues This reduced flow rate facilitates the counter current mechanism and water handling by the kidney because a higher flow rate would wash out the osmolal gradient required for water reabsorption and concentration of the urine [2,3] The rather precarious blood flow

volume deficit due to hemorrhage burns diaphoresis fluid sequestration in traumatized tissue or the gastrointestinal tract prolonged vomiting diarrhea or gastrointestinal drainage In the last decade the extremely potent loop diuretics furosemide and ethacrynic acid have made overzealous diuretic therapy one of the more common causes Frequently such patients show physical signs of volume depletion but these may be difficult to detect The diagnosis is suggested by the character of the urine which reveals an appropriate response to the physiological stimulus of volume depletion There is a high urine osmolality and specific gravity a very high concentration of creatinine and other nonreabsorbably solutes and a low concentration of sodium The diagnosis is established when the patients respond with a diuresis to appropriate therapy—prompt replacement of the volume deficit

Few renal responses have been more carefully studied than that to a volume deficit A reduction in renal blood flow and glomerular filtration rate occurs mediated in part by sympathetic nervous system activity[3] and possibly in part by activation of the renin angiotensin system With a severe deficit blood flow may be reduced to one third of normal despite a well maintained arterial pressure

In this setting the pathogenesis of the reduction in renal function is relatively well understood Sufficient afferent arteriolar constriction occurs that glomerular capillary hydrostatic pressure is inadequate to maintain filtration at normal levels Reduced renal function is due to renal ischemia i e a reduction in renal blood flow but is not due to an inadequacy of metabolic function of the renal parenchymal cells Rather the failure of function reflects a biophysical phenomenon—inadequate hydrostatic pressure delivery to the glomerular capillaries

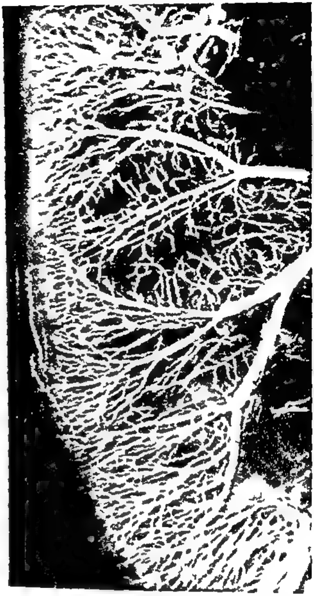

Fig 3C In the injected specimen obtained post mortem the vessels are normal as they were on histologic examination The arcuate and interlobular arteries are sharply demarcated and show no evidence of organic obstruction (From Hollenberg et al In Abrams H L. Angiography ed 2 Boston 1971 Little Brown & Company)

Acute oliguric renal failure states

During the past decade evidence has accumulated which suggests that the pathogenesis of the disruption of renal function in so called acute tubular necrosis also involves a critical abnormality of cortical perfusion A number of micropuncture studies in animal models recently reviewed by Oken have revealed a striking reduction in single nephron filtration rate associated with a reduced proximal tubular hydrostatic pressure These phenomena suggest that the cessation of glomerular filtration is attributable to inadequate capillary hydrostatic pressure In accordance with this interpretation direct morphologic examination with a variety of fixation techniques has revealed striking arteriolar vasoconstriction in such models[11]

Renal arteriography and xenon washout in patients with acute renal failure have revealed evidence of a selective profound reduction in

Fig 3 A and B This 54 year old woman had alcoholic cirrhosis and combined hepatic and renal failure (*A*) Arterial phase reveals a diminution in the caliber of the main renal artery and its intrarenal branches The arcuate arteries did not visualize (*B*) *The nephrographic phase reveals poor cortical flow and total absence of* corticomedullary differentiation The renal vein was not opacified (From Hollenberg et al *In* Abrams H L *Angiography ed 2 Boston 1971 Little Brown & Company*)

extent of recovery of renal function when this possibility exists arteriography must be carried *out as an emergency procedure*[5] *Reports of* return of renal function after renal artery embolectomy or reconstruction suggest that periods of *several days to several weeks may be tolerated by* the kidney if an adequate collateral blood supply for local nutrition is present An aortogram which reveals *filling of intrarenal vessels via alternative* routes despite total occlusion of the main renal artery suggests the presence of a collateral supply sufficient for this purpose *An illustrative arterio*gram from a patient with atrial fibrillation who developed an acute occlusion of the main renal artery to a solitary kidney due to a major embolus is shown in Fig 1 The patient presented with acute flank pain and anuria The kidney was viable despite a 30 hour history

Maintenance of viable tissue despite what must be a minimal blood flow delivery via tiny *preformed collateral vessels*[10] *probably reflects* the principles outlined above When filtration pressure is reduced to the point where filtration ceases *there is a striking reduction in renal* work and thus in renal oxygen requirement In the absence of tubular reabsorption of filtered sodium the oxygen requirement *of the kidney* becomes minimal

Pre-renal azotemia

The most common cause of an acute suppression of urine output and excretory function is functional secondary to a reduced cardiac output due to depletion of extracellular and plasma volume Generally pre-renal azotemia develops in a *patient in whom* the history suggests a

decade will be to define the mediators of the vascular events thus providing a clearer insight into pathogenesis and perhaps a new and specific approach to therapy

It is a pleasure to acknowledge the helpful discussions and comments provided by Drs John P Merrill Donald E Oken Eugene Braunwald Ramzi Cotran and Herbert L Abrams and the secretarial assistance provided by Miss Elaine Gorski.

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renal blood flow [8,9] The arteriographic features of acute renal failure (Fig 2) include severe attenuation of the intrarenal arterial tree, failure of visualization of cortical vessels, absence of the normal cortical nephrogram, and a striking reduction in the velocity of contrast transit through the kidney Xenon washout is characterized by the absence of the rapid component of xenon transit which is believed to reflect cortical perfusion in normal man The reduction in renal cortical perfusion to one third of normal if it involves primarily constriction of the afferent arterioles [13] is more than adequate to account for the cessation of renal function Again renal 'ischemia' results in failure of renal excretory function with a blood flow adequate to maintain renal parenchymal cell nutrition

The potential clinical utility of renal arteriography extends beyond the identification or exclusion of an acute vascular catastrophe [3] The arteriogram can be useful in discriminating between acute and chronic renal disease in discriminating acute parenchymal disease or vasculitis from acute renal failure in identifying renal cortical necrosis and in identifying acute renal venous obstruction [3]

A conceptually similar model has been applied to the hepatorenal syndrome, a common, frequently preterminal complication of advanced cirrhosis and hepatic failure [9] Progressive oliguric renal failure which differs functionally from acute tubular necrosis frequently develops in such patients Discrimination from acute tubular necrosis depends on the surprising ability to lower the urine sodium concentration and concentrate the urine despite progressive azotemia in the hepatorenal syndrome The urinary characteristics suggest a pre renal element but responses to a volume load tend to be incomplete and evanescent The abnormalities of the renal vessels defined by selective renal arteriography (Fig 3) and the characteristics of xenon washout in these patients also differ in several respects from those which characterize tubular necrosis In the hepatorenal syndrome the interlobar artery attenuation is especially striking and the vessels are extremely irregular The blood flow reduction is marked and remarkably labile suggesting the presence of a mediator which is capable of inducing intense phasic vasoconstriction The phasic blood flow abnormality and reversibility of the angiographic abnormalities (Fig 3) post mortem provide compelling evidence for active vasoconstriction in this syndrome

The morphologic lesion and its relation to ischemia

What of the tubular necrosis in 'acute tubular necrosis'? Does it reflect inadequate cellular nutrition? In experimental acute renal failure models, generally induced with nephrotoxins, there is frequently evidence of severe tubular necrosis [14] In patients with acute renal failure such gross distortions of structure are much less common and even electron microscopic studies may reveal only minimal damage [15,16] In one careful study experienced renal pathologists were unable to identify renal tissue from patients with 'acute tubular necrosis' when the sections were coded and presented in random order among sections from patients with normal renal function [17] Tubular necrosis is not as common or as widespread as our use of the term "acute tubular necrosis" would indicate

There are however patients in whom such lesions are clearly evident Either for a time during the initiation of the process blood flow was too low to maintain parenchymal nutrition or what we have come to call 'ischemic injury' may not reflect ischemia at all Suzuki and Mostofi [18] for example suggested that the tubular epithelial injury in a myohemoglobinuric model was primarily due to the local mechanical and chemical effects of heme crystals in the tubular lumina It is worth remembering moreover that a similar lesion occurs in response to a host of nephrotoxins where there is little evidence that suggests that they act through a direct effect on renal blood flow [14] Indeed tubular function is well maintained in the hepatorenal syndrome despite the striking reduction in renal blood flow to levels significantly lower than in acute renal failure and a similar morphologic lesion

Conclusion

Several lines of evidence suggest that failure of renal excretory and regulatory function in a number of common conditions is due to an abnormality of renal cortical perfusion which limits function not because of tissue hypoxia but rather because of inadequate hydrostatic pressure delivery to the glomerular capillaries In this setting renal angiography can provide useful clinical information The major challenge of the next

a significant natriuresis and kaliuresis persists for at least 24 hours When the same patients are given a single dose of furosemide the effect on natriuresis and kaliuresis persists for less than five hours This enhanced duration of action of metolazone [illegible] attributed to significant protein and red blood cell binding and enterohepatic recycling of the drug Metolazone in 1 mg doses is as effective an antihypertensive agent as 50 mg of hydrochlorothiazide and 100 mg of chlorthalidone [7] Furthermore at these dose levels there is no significant difference in the incidence of hypokalemia Metolazone offers no specific advantage over the thiazide diuretics in the treatment of hypertension A pharmacokinetic study of metolazone reveals that renal clearance of the drug falls by about 80 per cent in patients with severe renal disease when compared to normal subjects [8] Furthermore drug binding to plasma proteins decreases in the patients with severe renal disease Metolazone produces an effective diuresis in the treatment of chronic liver disease with ascites but the addition of a potassium sparing diuretic is generally necessary to avoid the high incidence of hypokalemia [9] Hepatic encephalopathy is also a significant complication in the treatment of chronic liver disease with metolazone probably because of the marked electrolyte disturbances that occur in these patients Therefore metolazone should be used cautiously in the treatment of chronic liver disease with ascites In patients with chronic renal disease high doses of metolazone cause a significant diuresis This is an advantage over the thiazide diuretics because of their ineffectiveness at low glomerular filtration rates A small number of patients with edema that are unresponsive to either furosemide or metolazone when used alone have a significant diuresis when both drugs are used together [12]

Aside from its use in chronic renal disease metolazone offers no distinct advantages over most other diuretics The toxic manifestations of metolazone are comparable to those of the thiazide diuretics

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Metolazone, a diuretic agent

Arnold Stern M D, Ph D *
New York N Y

Metolazone was recently introduced as a diuretic agent It is structurally related to the quinazoline sulfonamide series of diuretic agents and is considered a relatively potent, long acting diuretic and natriuretic agent with minimal kaliuretic activity Many of its pharmacological properties are comparable to the thiazide group of diuretics The purpose of this appraisal is to introduce the pharmacology of metolazone and to outline its clinical usefulness

Metolazone is generally given orally and is absorbed quite readily in the gastrointestinal tract Absorption is directly related to oral dose, except at very high dose levels where absorption is incomplete Maximum blood levels are reached between two and seven hours after oral administration Reversible binding to approximately 95 per cent occurs between metolazone and the red blood cells and albumin This enhances its duration of action because it is the free and unmetabolized drug cleared by the kidney that determines its diuretic effect[1] Metolazone excretion is primarily by filtration and secretion in the kidney but a significant amount of the drug appears in the feces following usual therapeutic doses because of enterohepatic recycling A single oral dose of metolazone is excreted in two to four days with 50 per cent excreted unchanged Metabolites of metolazone are mainly hydroxylated and then further oxidized by various mechanisms[1]

The prime site of metolazone action in the nephron is the cortical diluting segment where it blocks the reabsorption of sodium ions This is supported by the experiments with metolazone which show a decrease in free water generation during water diuresis[3] without a decrease in free water reabsorption during a hypertonic saline diuresis[4] Micropuncture and clearance studies indicate that metolazone also has a small but significant inhibitory effect on the proximal tubular sites of sodium and phosphate reabsorption[5] The decrease in sodium and phosphate reabsorption in the proximal tubule by metolazone is less than that of the thiazide group of diuretics Most diuretics decrease sodium and phosphate ion reabsorption in the proximal tubule because they inhibit carbonic anhydrase activity This decrease in the carbonic anhydrase activity is approximately proportional to the urine concentration of phosphate ions Metolazone causes a significant phosphaturia even though it has a relatively weak inhibitory effect on carbonic anhydrase activity[4] The exact mechanism of metolazone action in the proximal tubule remains unknown

Originally it was thought the metolazone would have a minimal effect on potassium excretion As more experience was gained under a variety of conditions the occurrence of hyperkaliuria associated with hypokalemia became evident Furthermore, in some patients that received metolazone potassium excretion exceeded sodium or water excretion This suggested that metolazone can cause a dissociation between potassium and sodium excretion, in a manner similar to ethacrynic acid Generally the greater the sodium load that appears at the distal tubular sites of sodium-potassium exchange the greater the output of potassium Since metolazone does not seem to function in this manner it has been suggested that metolazone either has separate effects on both renal sodium and potassium excretion or that an aldosterone effect persists[6]

When a single dose of metolazone is given intravenously to patients with edema and ascites

From the Department of Pharmacology Stella and Charles Guttman Laboratory for Human Pharmacology and Pharmacogenetics New York N Y

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Reprint requests to Arnold Stern M D Dept of Pharmacology Stella and Charles Guttman Laboratory for Human Pharmacology and Pharmacogenetics New York N Y 10016

*Assistant Professor of Pharmacology New York University School of Medicine

also that if edema was a cause of symptoms in hypertension the rate of edema formation and/or the amount of edema formed would be critical This suggestion is supported by data from human necropsy material suggesting that cerebral edema may have been present in hypertensives who never experienced encephalopathy

It was also noted that acute increases of blood pressure were only sometimes accompanied by cerebral vasoconstriction and that instead vessels might simply display partial autoregulation merely maintaining a constant diameter in the face of the elevated pressure head Such a phenomenon might account for superperfusion of the cerebral vasculature The latest conceptualization of the encephalopathy problem suggests that superperfusion may lead to edema and symptoms the former being produced by bulk transfer of excessive volumes of fluid passing through the vessels under high pressure The superperfusion has been called breakthrough" of autoregulation. What is meant is not merely an incomplete autoregulation as in the experimental studies cited above but actually a dilatation of vessels Interest would shift from supposedly narrowed vascular segments to dilated segments between them Indeed the question can then be raised as to whether some of the supposedly narrowed segments were merely segments of normal diameter positioned between dilated bead like segments Byrom has recently accepted at least as a possibility the hypothesis that dilation rather than spasm, is the key to encephalopathy in hypertension and has even recalculated data from hypertensive rats which indicates an increase rather than a decrease in the cerebral blood flow of these animals during the period prior to encephalopathy

Examination of cerebral blood flow (CBF) in human hypertensive patients may test the new hypothesis Both old and new studies suggest no fall in CBF unless encephalopathy has already occurred suggesting that the latter is cause rather than consequence of the declining flow In addition in studies of hypertensives whose pressures have been abruptly raised by drugs some subjects show an increased CBF in other words, an autoregulatory break through" On the other hand hypertensive patients also showed a vulnerability to pressure reductions, so that CBF fell and anoxic symptoms became apparent at pressures that would be innocuous in normal man. From the preceding it would appear that if a failure of autoregulation is the key to hypertensive encephalopathy it may also create dangers for successful therapy Obviously much work remains both to resolve the question of spasm versus dilation as a cause of encephalopathy and to define the limits over which blood pressure may be safely varied in hypertensive individuals

William I Rosenblum M.D
Division of Neuropathology
Medical College of Virginia
Richmond Va 23298

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Beta adrenergic receptor blockade and renal function

Beta adrenergic blocking drugs have become increasingly popular for the treatment of high blood pressure largely because of their apparent freedom from serious side effects Many of the occasional adverse effects of beta blockers have been recently summarized and these include bradycardia pulmonary edema bronchoconstriction hallucinations, drowsiness, depression sodium retention and the development of a positive antinuclear factor test Deterioration in renal function in patients with pre-existing renal failure must now be added to this list of possible side-effects and has been reported in three patients.

The three patients males aged 33 to 37 years, presented to a specialist renal unit over a period of six months All had chronic renal failure with hypertension and their blood urea concentrations six months before beta blockade was begun were in the range 60 to 100 mg per 100 ml. In spite of some variation in the effectiveness of blood pressure control, and episodes of postural hypotension in one patient renal function remained stable during the six months until treatment with beta blockers was begun but marked and in two cases irreversible deterioration in renal function followed the introduction of beta blockers

In the first patient propranolol was given in a dose of 120 mg. daily rising to 200 mg over nine days During this period

Annotations

What constitutes a Holter scan?

Holter electrocardiography is being employed with increasing frequency around the world by both general physicians and cardiologists In this technique a tape recorded electrocardiogram (ECG) is analyzed by a process usually referred to as scanning The scanning is the most critical step in the entire Holter technique and it is the responsibility of the physician who ordered the procedure to fully understand the methodology of how his particular tapes are scanned and the completeness reliability and reproducibility of such scanning

Initially scanning was usually performed by the physician himself and this provided him with a qualitative sense regarding the presence frequency and patterns of abnormalities contained on the tape even if his documentation (actual FCG strips obtained from the tapes with appropriate annotation) was incomplete However as demands for this technique have increased the practicing physician is usually unable to personally scan each tape In many hospitals or facilities this scanning function is now being performed by technicians coronary care unit nurses and occasionally medical students or house officers who have training and experience which may vary from negligible to superb The physician frequently has little knowledge regarding the background of the scan technician

Furthermore the physician is frequently presented only with documentation of the scan consisting of a stack of ECG strips or similar strips mounted on sheets of paper and is expected to prepare a descriptive Holter scan report from such strips It must be emphasized that it is impossible to obtain an accurate picture of the Holter tape contents from such isolated strips. For example if an ECG segment contains a ventricular extrasystole it could be the only extrasystole of that morphology present in an entire recording or it may be a morphologic example of an event occurring at different times with varying frequencies throughout the recording period Only the person who actually did the scanning knows which. In other words if the physician does not personally scan the tape the report to him must provide an appropriate descriptive summary with example documentation for each time segment encompassed in the recording This can be provided only if the scanning is done by very carefully trained analysts who are thoroughly familiar with ECG patterns and abnormalities and who follow carefully worked out procedures and methodologies comparable to the consistency and reliability that a physician expects when a blood chemistry is ordered

Holter electrocardiography is an invaluable tool to the general physician and cardiologist and physicians should not be misled perhaps with medical legal exposure by scanty or incomplete scan reports In the same way that the famous Peter Arno advertisement for vermouth stated A martini is not a hooker of gin physicians should realize that a Holter scan is not a stack of ECG strips

Daniel J Bleifer M D F A C P F A C C
Assistant Clinical Professor of Medicine
University of California
School of Medicine
Los Angeles Calif 90024

A renewed look at hypertensive encephalopathy

Hypertensive encephalopathy is a condition which is often diagnosed in patients displaying both high levels of blood pressure and either convulsions or evidence of diffuse cerebral malfunction Because of the presence of complicating factors such as renal failure the pathogenesis of signs and symptoms is often in doubt and in individual patients the existence of an encephalopathy based solely on an interaction between pressure levels and brain may be doubted Nevertheless it seems clear that a true hypertensive encephalopathy does exist and that such encephalopathy is reversed by timely reduction of blood pressure Recently the causes of such encephalopathy have come under intensive review Since effective prevention and therapy should ultimately rest on clear and correct concepts of pathogenesis a brief review of the newer thinking seems appropriate

Byrom s classical hypothesis suggested that encephalopathy was caused by ischemia and consequent edema The ischemia was ascribed to cerebral vasospasm which was in turn produced by high pressure levels In this hypothesis vasospasm was the key Normally vessels undergo autoregulatory vasoconstriction when pressure rises so that cerebral blood flow remains constant Byrom postulated that in some hypertensive patients this response was exaggerated thus producing vasospasm and ischemia It is this suggestion and the central role of vasospasm which may require re evaluation In addition it is necessary to review the hypothesis linking ischemia to edema

For several years evidence has been available that in hypertension cerebral edema may be observed without evidence of vasospasm [2] Evidence of edema was demonstrated ultrastructurally as well as grossly and by analysis of brain water content Such edema could be found without indication of cerebral malfunction [4] Thus the evidence suggested not only that edema could be dissociated from vasospasm but

also that if edema was a cause of symptoms in hypertension the rate of edema formation and/or the amount of edema formed would be critical This suggestion is supported by data from human necropsy material suggesting that cerebral edema may have been present in hypertensives who never experienced encephalopathy

It was also noted that acute increases of blood pressure were only sometimes accompanied by cerebral vasoconstriction and that instead vessels might simply display partial autoregulation merely maintaining a constant diameter in the face of the elevated pressure head Such a phenomenon might account for superperfusion of the cerebral vasculature The latest conceptualization of the encephalopathy problem suggests that superperfusion may lead to edema and symptoms the former being produced by bulk transfer of excessive volumes of fluid passing through the vessels under high pressure The superperfusion has been called breakthrough" of autoregulation What is meant is not merely an incomplete autoregulation as in the experimental studies cited above but actually a dilatation of vessels. Interest would shift from supposedly narrowed vascular segments to dilated segments between them Indeed the question can then be raised as to whether some of the supposedly narrowed segments were merely segments of normal diameter positioned between dilated, bead like segments Byrom has recently accepted at least as a possibility the hypothesis that dilation rather than spasm, is the key to encephalopathy in hypertension and has even recalculated data from hypertensive rats which indicates an increase rather than a decrease in the cerebral blood flow of these animals during the period prior to encephalopathy

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William I Rosenblum M D
Division of Neuropathology
Medical College of Virginia
Richmond Va 23298

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Beta adrenergic receptor blockade and renal function

Beta adrenergic blocking drugs have become increasingly popular for the treatment of high blood pressure largely because of their apparent freedom from serious side effects Many of the occasional adverse effects of beta blockers have been recently summarized and these include *bradycardia* pulmonary edema, bronchoconstriction hallucinations, drowsiness depression sodium retention and the development of a positive antinuclear factor test *Deterioration* in renal function in patients with pre-existing renal failure must now be added to this list of possible side-effects and has been reported in three patients.

The three patients, males aged 33 to 37 years, presented to a specialist renal unit over a period of six months. All had chronic renal failure with hypertension and their blood urea concentrations six months before beta blockade was begun were in the range 60 to 100 *mg per 100 ml* In spite of some variation in the effectiveness of blood pressure control, and episodes of postural hypotension in one patient renal function remained stable during the six months until treatment with beta blockers was begun but marked and in two cases irreversible deterioration in renal function followed the introduction of beta blockers

In the first patient propranolol was given in a dose of 120 mg. daily rising to 200 mg. over nine days During this period

the plasma creatinine concentration rose from 2 1 to 5 4 mg per 100 ml Propranolol was withdrawn and the plasma creatinine fell to pretreatment levels within a few days In the second patient propranolol was given in a dose rising from 120 to 240 mg daily over 10 weeks The plasma creatinine which had been stable for six months at about 2 5 mg per 100 ml rose during this period to 13 0 mg per 100 ml Withdrawal of the drug did not result in return of renal function to normal and failure of conservative management led to establishment of the patient on the chronic hemodialysis program The third patient received oxprenolol 120 mg daily for 20 days during which time his plasma urea concentration rose from 132 to 390 mg per 100 ml After withdrawal of the drug no improvement in renal function occurred and intermittent hemodialysis became necessary

In the first patient a beta blocker was introduced because postural hypotension had developed with methyl dopa and in the remaining two patients a beta blocker was used as an adjunct to antihypertensive therapy None of the patients had developed accelerated hypertension when renal function began to deteriorate neither had there been any significant changes in the degree of blood pressure control during that period In none of the patients was there evidence of infection urinary tract obstruction exposure to nephrotoxic drugs or any other cause for deterioration in renal function It was concluded that the observed deterioration in renal function may have been caused by beta blocking drugs and the authors recommended that they should not be used in patients with moderately severe renal failure It may be significant that the patients in whom beta blockers appeared to cause irreversible deterioration in function had been treated with the drugs for much longer periods than the patient in whom deterioration in function was reversible

There is now a considerable body of evidence to suggest that beta blockers reduce renal blood flow and glomerular filtration rate and these effects are common to several antihypertensive agents which cause reduction in cardiac output Reduction in cardiac output occurs after intravenous and oral propranolol Both renal blood flow and glomerular filtration rate fall following propranolol administration in acute experiments and oxprenolol causes a reduction in glomerular filtration rate Reversible reduction of 13 per cent in glomerular filtration rate following long term administration of oral propranolol to hypertensive patients has also been recently demonstrated This reduction in glomerular filtration rate would not be reflected in a significant rise of blood urea in patients with normal renal function but in patients with preexisting chronic renal failure a small reduction in glomerular filtration rate would cause a large increase in blood urea concentration These effects of propranolol on renal function appear to be secondary to changes in systemic hemodynamics Intravenous injection of propranolol in dogs causes a decrease in renal blood flow and glomerular filtration rate but no effects were observed when propranolol was infused into one renal artery

The possibility that beta blockers cause deterioration in renal function is important in the light of two recent developments First propranolol has been recommended as the treatment of choice in patients with renal hypertension and high plasma renin activity and a recent leading article recommends the combination of a beta blocker and a vasodilator as an alternative to nephrectomy in renal hypertension [11]

Second a high incidence of atherosclerotic heart disease and myocardial fibrosis has been shown in patients with chronic renal failure It is, therefore possible that among patients with chronic renal failure there is a sub population particularly susceptible to the negative inotropic and chronotropic effects of beta blockers on the heart This view is supported by a recent report from the Boston Collaborative Drug Surveillance Program of a threefold increase in the incidence of adverse reactions to propranolol among patients whose blood urea nitrogen concentration was more than 25 mg per 100 ml, when compared with those with a blood urea nitrogen concentration of less than 25 mg per 100 ml

Detailed studies of the effects of beta blockers on renal function in patients with chronic renal failure are needed to determine the safety of these agents When their use is judged by the physician to be indicated in spite of possible adverse effects in patients with renal failure then renal function should be closely monitored

Dr David J Warren BM D Phil MRCP
Department of Medicine
Royal Infirmary
Edinburgh Scotland

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Of soup

Proper water and electrolyte balance is necessary for good health. Unfortunately quite frequently ill health is produced by or associated with water and electrolyte imbalance The physician becomes obligated to rectify this imbalance by therapy Such therapy is conducted with solutions available in hospitals When 5 per cent glucose in water is used i.e a solution with 5 000 mg of glucose per 100 ml of water all substances in the body electrolytes included are diluted except glucose With such a solution 5 000 mg of glucose per 100 ml of fluid are added to blood containing 100 mg of glucose per 100 ml If that is the therapy the *physician desires* or if it is satisfactory for the patient only then is it good therapy When physiologic saline solution 0 85 per cent NaCl in water (a most unphysiologic solution) is used then all substances in the body except Na and Cl *are diluted If that is* what the physician desires for his patients then it may be all right. This argument can be applied to some *extent to all other* fluid used in therapy today for electrolyte and water replacement. When loss of fluid is through *diarrhea fistulas* vomiting or other disturbances in which substances lost include almost all substances of the body fluids *and certainly* all electrolytes and elements that are found in man then *soup* certainly is the only ideal replacement fluid *Man is made of* tissue with intra and extracellular substances of many sorts (many still unknown) and so is vegetable soup Soup intake is merely an "infusion" of animal and plant tissue with essentially the same intra and extracellular substances as found in the body fluids of man It contains most if not all the elements of this earth, and so does man and so does diarrheal fluid Therefore soup is *the most ideal fluid for replacement of* water and "electrolyte" or body fluid deficiency Soup should then be used *to replace* body fluids whenever possible The results are astounding and the patient is impressed especially when soup is used to replace diarrheal fluid It must be admitted that such therapy is *not fancy and is usually less* impressive to the patient s family than an *intravenous "drip* Unfortunately soup can be administered *orally* or by gastric tube *only The* administration of soup in therapy may *carry a* stigma of being archaic but *the fact that it is not fancy* or modern is of no consequence After all *antiques* and articles of *antiquity are not* modern but when compared in price with modern arti les, *they are precious*

Soup is a truly physiologic fluid which is readily available and it should be used whenever *feasible* to correct certain *types of water and electrolyte* deficiencies

George E Burch M.D
Tulane University School of
Medicine and Charity Hospital
New Orleans La 70112

Letters to the Editor

The peripheral circulation in borderline hypertension

To the Editor

The article by Dr Safar and co workers (AM HEART J 89 480-486 1975) constructively shifts focus from the heart to the neglected peripheral circulation in examining the elevated cardiac output (CO) in borderline hypertension A part of their contribution depends upon the demonstration that cardiopulmonary blood volume (CPBV) and CPBV/TBV (total blood volume) are elevated in borderline hypertensive patients a point which invites further consideration The central mean transit time (MTT) from pulmonary artery to aortic root was used in estimating CPBV That time while not given by the authors may have varied relatively little in different patients if they had normal central circulations If so this would make CPBV almost entirely dependent upon CO and would render a strong positive correlation between CPBV and CO obligatory Use of the central MTT prevents the peripheral circulation which is the focus of study from contributing to the MTT and thereby prevents the derived CPBV from revealing disproportions in peripheral flow which might expose the vascular segment responsible for the high venous return found by the authors in their borderline patients

The authors might consider using peripheral sampling sites in future studies For example if the dye curves were sampled from the brachial artery and consequently the MTT reflected the velocity of flow to that type of circulatory bed an increase or a decrease in CPBV (now a different and somewhat larger volume) would reveal that cardiac output and therefore venous return were dominated by another circulatory bed elsewhere to which the MTT was shorter (increased CPBV) or longer (decreased CPBV) than the time to the brachial artery On the other hand if flow velocities (MTTs) throughout the periphery varied *equally* with an abnormality such as permanent hypertension perhaps or with an intervention such as certain vasoactive infusions perhaps CPBV would not change if a peripheral sampling site were used because changes in CO and MTT would always be proportionately but inversely related The unchanging CPBV itself would reveal the fact that major variations had been equally distributed throughout the peripheral circulation

The intriguing aspect of the use of a peripheral sampling site or better still of the possible use of multiple sampling sites including mesenteric and renal arteries is the potential they may have as tools for attacking such problems as the identification of the particular vascular bed providing the high venous return in hypertensive patients with a high CO or for the study of the peripheral effects of interventions which may influence the CO in any patient

This view of the CPBV and the MTT the basis of which is well established[1] may be worth applying to further studies of the peripheral circulation in hypertension

John M Wallace MD
Professor of Medicine
University of Texas
Medical Branch
Galveston Texas and
Visiting Professor of Medicine
Cardiovascular Center
Cornell University
School of Medicine
New York N Y

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Borderline hypertension and norepinephrine

To the Editor

I read with interest the American Heart Journal article entitled Vascular reactivity to norepinephrine and hemodynamic parameters in borderline hypertension by Safar and colleagues (AM HEART J 89 480 486 1975) I think the authors present interesting observations and I agree that their data supports their basic findings namely that in the borderline hypertensive patients studied the pressor dose of norepinephrine is increased and that this increase correlates to the basal cardiopulmonary blood volume However I feel that their further discussion of the role of sympathetic pharmacology in labile hypertensive patients is not supported by their data in terms of adrenergic receptor and clinical pharmacology

In specific although drug doses are calculated per kilogram of body weight plasma concentrations of drugs are not measured Thus the variability of the relationship of drug dose to

plasma concentration is ignored Although the intravenous use of these drugs simplifies this problem somewhat a large variable the volume of drug distribution is unmeasured There is no reason to believe that the volume of drug distribution is equal between the three clinical classes of patients studied Indeed the authors themselves have shown significant difference in blood volume and distribution between the patient groups suggesting that the volume of drug distribution may also vary Thus, the drug dose to blood pressure response relationship presented cannot be construed to be equivalent to a drug concentration to response relationship and thus conclusions regarding receptor pharmacology become tenuous Furthermore to interpret changes in alpha adrenergic receptor pharmacology meaningfully concentration to response relationships must be complete—that is curves constructed using drug concentrations resulting in subthreshold to maximal responses must be used—and the results should be normalized Obviously maximal pressor doses of norepinephrine are incompatible with human experimentation however short of such data conclusions again are not well founded Furthermore in order to compare drug doses which are needed to reach a given response level that response level must be demonstrated to be within the linear portion of the drug concentration to response relationship The potential of comparing points at threshold values that are slow rising versus later points which are on the rapid rising linear portion of the dose response curve invites misinterpretation

The authors conclusion that a decreased responsiveness to norepinephrine in borderline hypertensive patients suggests the possibility of a change in the role of availability of receptor sites to the vasoactive agent may be indeed correct however their inferences from this point are incompatible with adrenergic receptor pharmacology A decrease of available receptor sites implies a competitive or noncompetitive alpha adrenergic receptor antagonist Alternatively a physiologic antagonist might give similar results However I know of no evidence that shows that norepinephrine can physiologically or pharmacologically antagonize itself Indeed if a patient s vascular system were stimulated by pre-existing endogenous norepinephrine as the authors suggest additional increments of exogenous norepinephrine should give a greater increment of vascular response since such a system would *not* be operating on the early threshold portion of the dose response curve but rather on the linear rapid rising portion of this relationship Since the authors own observations show exactly the opposite that is a greater amount of norepinephrine is needed to evoke a similar response their conclusions seem unsupported by their data

I realize that the above pharmacologic considerations can rarely if ever be met in human experimentation However in a paper which cites receptor pharmacology and an altered response to vasoactive *agents* as a prime pathophysiologic determinant in borderline hypertensive patients I think that it is important that the above concepts be included in the interpretation of the data Although the authors interpretations are frequently qualified by the word "suggests, I would prefer their stating *clearly* where their inferences do and do not meet strict receptor and clinical pharmacologic principles This information is not always readily available to or remembered by the active clinician The information, however is essential to the proper interpretation of articles dealing with cardiovascular pharmacology as this one does.

I would be most interested in the editor s and/or authors comments in regard to the above critique and in the above concepts of clinical and receptor pharmacology being published either as the letter above or in terms of an editorial by an expert of your choice

Kenneth M Kessler M D Major MC
Formerly Assistant Chief General Medicine Service
Brooke Army Medical Center
Fort Sam Houston Texas 78234
Present address Dept of Medicine
Temple University Health
Sciences Center
Philadelphia Pa 19140

Autoauscultation in a patient with floppy mitral valve syndrome

To the Editor

Laennec named the method of listening with the aid of a stethoscope mediate" auscultation to distinguish it from immediate auscultation which was performed by placing the listener s ear on the body of the patient "Autoauscultation " an older kind represents what a person hears of sound emanating from his or her body Hearing one s heart sounds is a very common experience which usually occurs while lying in bed on the left side with the chest and the ear on a continuous surface pillow or mattress. In some rare instances patients hear heart murmurs while they are in sitting or standing posture These murmurs may be *transient and usually represent* a significant valvular abnormality In 1880 William Osler published his observations on "a remarkable heart murmur heard at a distance from the *chest wall* " The following excerpts from this article are quoted because they describe clinical features which resemble those of our patient

"J W aged twelve a well nourished young girl was sent to me in May 1880 by Dr Buller who had noticed a remarkable whistling sound while examining *her eyes* The mother stated she had been a healthy child though never robust Had inflammation of the lungs at eighteen months measles at the age of 3 and scarlet fever three years ag Auscultation—As she sits upright *in the chair* the heart sounds at the apex and the base loud and clear no murmur When she stands a loud systolic murmur is heard at the apex high pitched somewhat musical, of maximum intensity in fifth interspace it varies a good deal being loud for three or four beats and then faint for one or two succeeding ones due to the influence of *respiration On removal of the* ear from the chest wall, the murmur can be heard at a distance of several inches It disappeared quite suddenly and could not be detected on most careful examination She was then asked to run about the room and up and down stairs. On sitting down after this the heart s action was very forcible but the heart sounds were clear The child then suggested that she heard it most frequently when in the stooping posture and on causing her to lean forward and relax the chest the murmur was at once heard and with greatly increased intensity It was distinctly audible at a distance of three feet two inches by measurement and could be heard at any point on the chest and on top of the head Pulse 96

*The first Professor of Ophthalmology at McGill University

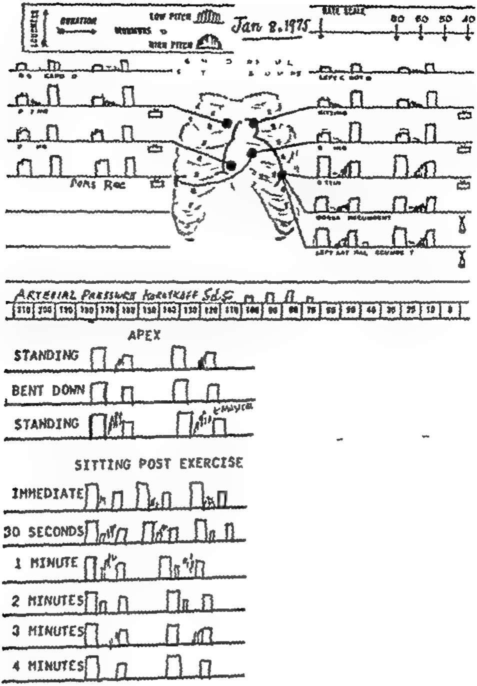

Fig 1 Quantitative symbol phonocardiogram (QSPcg) depicts the normal pattern of heart sounds with respect to loudness *duration and quality* The late crescendo coarse systolic murmur was the first clue to the diagnosis of floppy mitral valve syndrome Auscultation at the apex with the patient standing then bent forward touching her toes *with her fingers then again in the standing position* seems to have elicited a quite loud musical crescendo systolic murmur which however was not loud enough to be audible by the patient who did not hear any murmur during the entire study *The exercise consisted of 40 mountings of the* two step in 90 seconds raising the heart rate to about 150 per minute A significant somewhat superficial and musical murmur appeared 30 seconds after exercise and grew a little louder until the second minute when no murmur but the early systolic click (a short sound) which appeared at 30 seconds persisted This too disappeared in the third minute when the late short crescendo-systolic murmur reappeared But this too disappeared in the *fourth minute* leaving only the normal first and second sounds When the patient was examined again on February 10 1975 the only abnormal feature was a faint short early click about *half as loud* as the one heard on January 8th These observations emphasize the wide unpredictable variability of the systolic click and murmur which point to the diagnosis of a floppy mitral valve The QSPcg written while listening contains precise details some of which could not be found in an electrophonocardiogram (EPcg) e g the superficial musical quality of the systolic murmur the distinction between the coarse quality of the crescendo murmur before exercise and the blowing quality immediately after exercise On the other hand the electrophonocardiogram (EPcg) would permit precise measurement of the time interval between the first sound and the click (Diagram adapted and modified from Segall Harold N in Encyclopedia of Cardiology Luisada A A ed New York 1959 McGraw Hill Book Company Inc Vol 1 p 3 105)

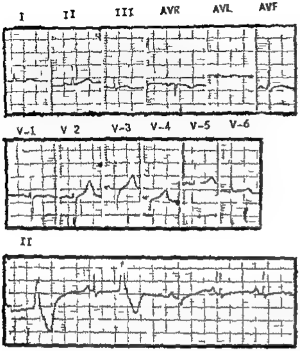

Fig 2 Lead II recorded *after exercise* reveals occasional ventricular ectopic beats

On May 28th she was shown at the Medico Chirurgical Society of Montreal and most of the members heard the murmur. A day or two before the meeting I called at her mother's house and satisfied myself of its presence though it was very variable.

On July 13 I saw her again at her home and failed after prolonged examination to hear the murmur. She stated that she had not heard it herself for some time. When he examined her on July 21 he did hear the murmur and added that "There was no constancy in the variations. The rhythm is distinctly systolic, the first sound of the heart is not effaced by it though not so sharp as in its absence. During an examination extending over twenty minutes the murmur was present four or five times and for a brief interval only, less than a minute each time." It is tempting to continue quoting Osler's remarks and his discussion of the literature which he ends with the following: "I am not prepared to suggest an explanation of the cause of the murmur in this instance" and he adds that his patient was "delicately built and nervous."

The person who reported Osler's presentation of the case at the Medico-Chirurgical Society of Montreal wrote the following: "Dr Osler cannot account for the murmur but thinks, perhaps, it arises from an unusually flexible chest and pressure thus exerted on the pulmonary artery and aorta. Dr Ross† suggested that it might possibly be explained by the existence of some loosely pedunculated body hanging inside the heart in such a way that, only in certain positions it would

Fig 3 In the dorsal recumbent posture the interval between the beginning of the first sound and of the click varies between 200 and 210 msec. In the sitting posture it varies between 240 and 260 msec. The amplitude of the sound waves do not precisely reflect the relative loudness of the sounds heard with the stethoscope as depicted in the quantitative symbol phonocardiogram (QSPcg). Clinical auscultation affords a clearer distinction between the late crescendo systolic murmur and the second sound than the electrophonocardiogram (EPcg).

An error has crept into the records of the date of this meeting: Osler gives May 28, 1880; this report uses April 30th.

†Dr George Ross.

fall into the blood current and develop a murmur The *President rather favoured the idea that it was most likely due* to bending of the costal cartilages and pressure on the pulmonary artery"[2]

Our patient V H (ECG #61496) a young woman of 23 heard a peculiar noise emanating from inside her chest at the age of twelve She remembers that one day when at home seated and in the company of several friends she became aware of a peculiar squeaking grating noise a rhythmically *recurring noise emanating from her chest She could listen to* the conversation while hearing this noise which soon disappeared During the next ten years it recurred occasionally At the age of eighteen she consulted a physician because she noticed irregularity in her heart beating The physician reassured her and recommended abstinence from tea and coffee She has never smoked cigarettes or any type of tobacco The irregularity continued to recur and in addition the noise began to appear with gradually *increasing frequency During the* past year or so she heard the noise once in many weeks then the intervals shortened to about two weeks then several times a week and more recently she has been hearing it several times a day She has never heard it while in bed or otherwise recumbent In search of some correlation with a particular activity she has noticed that it tends to come on when she is standing in the kitchen and vigorously stirring a mixture of food she is preparing Emotional excitement also tends to elicit the noise It is invariably regular in rhythm Sometimes it stops for only a few beats then starts again and continues for *some minutes when it stops and becomes audible again only* the next day or several days later She feels the cardiac irregularity independently of the noise When she consulted Dr Lawrence Battersby recently he heard the noise the first physician who did hear it and he referred her to us for further study

About two months previously she asked her boyfriend to place his ear on her chest when she was aware of the noise and he confirmed that *it accompanied each heart beat*

Both parents her brother and sister are in good health Having in mind a recent experience with twin males aged 6? *both of whom have the floppy mitral valve syndrome and each* of whom has one son who also has this condition we invited her parents and siblings to be examined They declined apparently without regrets *She has not had any major illness* in the past She did have measles and chicken pox as a child and influenza at nineteen She works as a clerk in the library of an industrial firm

Physical examination A slender delicate young woman of 23 weight 91 pounds height 63 inches Nothing could be found to suggest Marfan syndrome No abnormalities could be detected until the heart murmurs were heard

The pattern of heart sounds the heart murmurs and Korotkoff sounds are described more precisely more completely in greater detail by the quantitative symbol phonocardiogram *(QSPcg) in Fig 1 than any description in language* could achieve The electrophonocardiogram (EPcg) in Fig 2 confirms variations in time relationship of the click

The electrocardiogram (Fig 3) presents only normal features before exercise but after forty mountings of the two step exercise test two ventricular premature beats were recorded

X ray film of the chest revealed no abnormalities The following report was received from Dr F Winsberg of the Montreal General Hospital about the ultrasound study

Echocardiogram shows a classic midsystolic buckling of the mitral valve This is the sort of prolapse which produces the midsystolic click—late systolic murmur pattern There is no *evidence of chamber enlargement*

Eighty five years separate Osler's observations from ours. His vivid description strongly favors the view that his patient had a floppy mitral valve Had he remained in Montreal during the next 39 years of his life we might have had an interesting follow up report on that patient At present the technique of echocardiography makes possible a good correlation between the physical signs and the diagnosis of the *anatomical and physiological anomaly From the experience* with other patients notably with one of the twins mentioned above we have learned that wide variations in the pattern of sounds and murmurs occur in some cases The transient character of the typical signs accounts for the fact that when our patient was examined annually at school and before going to camp no physician noted a significant abnormality until Dr Lawrence Battersby happened to listen when the systolic *click and murmur* did appear The autoauscultation feature makes the clinical story of this patient of special interest Osler's case of 95 years ago gains in significance in the light of *current use of echocardiography*

Our speculations about the cardiodynamics which result in the absence the appearance disappearance and reappearance of the click and murmur in so wide a variety of loudnesses, durations and qualities would resemble in accuracy the speculations of Osler Ross and Howard about the origin of the murmur

The author wishes to express his cordial thanks to Dr Lawrence Battersby who introduced the patient to him and to Dr F Winsberg who did the echocardiogram

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1 Laennec R T H Traité de l auscultation médiate et des maladies des poumons et du coeur 4th ed J S Claudé Paris 1837 vol 1 10
2 Osler W On a remarkable heart murmur heard at a distance from the chest wall *Med Times and Gaz Lond* ii 432 433 1880 Patient presented Medico Chirurgical Society of Montreal April 30 1880 Reported in Can *Med Surg J VIII* 518 519 1879 1880
3 Segall H N Use of written symbols to describe cardiovascular sounds and murmurs *in* Encyclopedia of Cardiology Luisada A A ed McGraw Hill Book Company Inc vol 2 p 3 105 1959
4 Segall H N Evolution of graphic symbols for cardiovascular sounds and murmurs Br Heart J 24 1 1962

Book reviews

Advances in Microcirculation, vol. 6. Edited by H. Harders. Basel, 1975, Karger AG. 153 pages. Price $41.00.

This sixth volume on Advances in Microcirculation is concerned with hyperviscosity syndrome in plasma cell dyscrasias, pathophysiology and clinical aspects of capillary resistance and the hepatic microcirculatory unit. The three sections by Somer, Kramer, and Rappaport, respectively, are well written and important isolated aspects of the microcirculation. The microcirculation is generally ignored by clinicians, but it is this part of the vascular system which is in direct contact with all cells and is responsible for their health and function. Although this may be considered a highly specialized subject, it is extremely important and reflects important fundamental aspects of the blood supply to tissues. This is an excellent publication.

Acute Aortic Dissections. By C. E. Anagnostopoulos, C. L. Athanasuleas, T. R. Carrick, and R. Paulissian. Baltimore, 1975, University Park Press. 285 pages. Price $24.50.

This is a very good book on the problems of dissecting aortic aneurysms. The presentation is good and the book is well organized. The embryology and anatomy are nicely presented. Readers will find the discussion of hemodynamic aspects very provocative. The illustrations are clear and well selected. The management of this relatively rare disease should interest all cardiologists and cardiovascular surgeons. This is a very useful book and it is highly recommended as a good single publication on an important subject.

Practical Management of Hypertension. Edited by G. L. Wolf and R. S. Eliot. Mount Kisco, N. Y., 1975, Futura Publishing Company. 214 pages. Price $14.95.

This small book edited by Wolf and Eliot briefly reviews in 11 short chapters the clinical care of patients with hypertension. Because each chapter is written by a different author, the family physician, for whom the book is intended, will find it difficult to integrate properly the concepts and plans outlined in each chapter. This rather disconnected approach will not save much time, if any, as compared to a single even smaller monograph by an experienced clinician who has been successfully treating patients with hypertension. The book is interesting and each chapter well written, but the busy doctor, it seems to this reviewer, would have preferred a more specific single authored approach to the management of patients with high blood pressure. This book does contain important useful information, however, which is clearly presented.

Contrasting Concepts of Ischaemic Heart Disease. By Gunnar Biorck, M.D., F.R.C.P. Stockholm, Sweden, 1975, Almqvist & Wiksell International. 138 pages.

This publication contains the two 1974 Lilly Lectures delivered by Gunnar Biorck at Oxford and London. They are on ischemic heart disease, the first being concerned with ischemic heart disease as a medical and psycho social disease and the second about ischemic heart disease as a disease that should concern everyone as a serious public health problem. Biorck's two lectures are rich with important epidemiologic data and evidence to support factors which are considered at present to predispose to arteriosclerosis. The tables and figures summarize extremely well the seriousness of ischemic heart disease which, in spite of all efforts, is a plague-like disease even today. These two lectures are extremely important and *the data should interest all people, not only physicians and other health professionals, but granting agencies and governments all over the world.*

Recent Trends in Cardiovascular and Thoracic Surgery. Edited by Joseph B. Borman, M.B. New York, 1975, Grune & Stratton, Inc. 22? pages. Price $17.50.

This book edited by Borman consists of a series of papers on the surgical treatment of congenital, rheumatic, and ischemic heart diseases and also cardiac transplantation, lung and esophageal surgery, and vascular surgery. The numerous contributors are outstanding surgeons who summarize very well the long term results and follow up of surgically treated patients. The follow up data on ischemic heart disease are not adequate yet. The selection of patients for surgery for coronary heart disease and the satisfactory matching of surgically and medically treated patients for evaluation of results are still needed. This publication does summarize the results of experienced surgeons. The reader interested in surgical procedures for the care of their patients with heart disease will find a critical study of this book to be profitable.

The Human Heart: A Guide to Heart Disease. Edited by *Brendan Phibbs, M.D.*, Saint Louis, 1975, The C. V. Mosby Company. 280 pages. Price $7.50.

This paperback book on the heart and its common diseases edited by Phibbs is *for patients and other laymen. By means of* simple illustrations and explanations the patient will learn from this book the many questions which surface in his mind concerning the heart, how to prevent heart diseases, and how and why he should follow the therapeutic measures outlined for him by his physician. There is a need to let patients know why they are advised to do certain things and use certain drugs for their heart ailments. This book is not expensive, it is clearly written, and will save the busy physician a great deal of time in explaining to patients why the therapeutic measures are prescribed. However, illustrations of a man using an air hammer, climbing a mountain, or painting a house on page 196 in a chapter on pregnancy and heart disease is puzzling to this reviewer. Illustrations of types of exertion applicable to the pregnant housewife would be more appropriate. Nevertheless, this is a good book for patients who want to know about their heart disease and treatment.

fall into the blood current and develop a murmur. The President rather favoured the idea that it was most likely due to bending of the costal cartilages and pressure on the pulmonary artery.

Our patient V R (FCG #64 496) a young woman of 23 heard a peculiar noise emanating from inside her chest at the age of twelve. She remembers that one day when at home seated and in the company of several friends she became aware of a peculiar squeaking grating noise a rhythmically recurring noise emanating from her chest. She could listen to the conversation while hearing this noise which soon disappeared. During the next ten years it recurred occasionally. At the age of eighteen she consulted a physician because she noticed irregularity in her heart beating. The physician reassured her and recommended abstinence from tea and coffee. She has never smoked cigarettes or any type of tobacco. The irregularity continued to recur and in addition the noise began to appear with gradually increasing frequency. During the past year or so she heard the noise once in many weeks then the intervals shortened to about two weeks then several times a week and more recently she has been hearing it several times a day. She has never heard it while in bed or otherwise recumbent. In search of some correlation with a particular activity she has noticed that it tends to come on when she is standing in the kitchen and vigorously stirring a mixture of food she is preparing. Emotional excitement also tends to elicit the noise. It is invariably regular in rhythm. Sometimes it stops for only a few beats then starts again and continues for some minutes when it stops and becomes audible again only the next day or several days later. She feels the cardiac irregularity independently of the noise. When she consulted Dr Lawrence Battersby recently he heard the noise the first physician who did hear it and he referred her to us for further study.

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4. Segall H N. Evolution of graphic symbols for cardiovascular sounds and murmurs Br Heart J 24 1 1962

American Heart Journal

March 1976 Volume 91 Number 3

Editorial

Possible reasons for the comparatively high resistance of women to heart disease

Stephen Seely B Sc
Sale Cheshire Gt Britain

The comparatively high resistance of women to occlusive coronary disease is a well known but still unexplained phenomenon It is usually attributed to the effect of estrogens or heavier smoking alcohol consumption or more occupational stress by men The least justified of these is probably the assumption that estrogens have a beneficial effect on vascular disease as evidence can be found to support the opposite view Notably the administration of estrogens to men—mainly for the relief of prostatic cancer—has been found to aggravate coronary disease and experience with oral contraceptives also points to previously unsuspected adverse effects The possible effects of smoking alcohol and stress will be discussed later

This article presents a new hypothesis generally based on the often heard suggestion that some fault of cholesterol metabolism is involved in the pathogenesis of atheroma The relevant aspect of the assumed metabolic error is that the faulty metabolites are difficult to eliminate from the blood stream It will be pointed out later that women have a channel of disposal capable of dealing with a small quantity of noxious substances which men lack This may be the basis of their comparative immunity

Statistical data concerning male and female resistivity to vascular disease

Fig 1 shows male and female mortality rates from ischemic heart disease and cerebrovascular disease for the white population of New York State in 1969[1] Comparable data for England and Wales for the year 1971 are shown in Fig 2[2] The points shown dotted in Figs 1 and 2 represent the yearly averages of the quintennial figures published in the quoted sources divided by the number of male or female population living in the country in the year under review White population only was taken in New York State the total population in England and Wales The object of these graphs is to present typical male and female mortality rates in easily surveyable form hence they are shown as smooth curves The disadvantage of such unprocessed statistics is that they show the correct relationship between male and female mortality rates only up to the onset of old age namely while the male and female population of the country is roughly equal In old age women greatly outnumber the still surviving group of men and the correct correlation of their mortality rates requires a more elaborate treatment The present article examines mortality rates only up to early old age

Let us consider ischemic heart disease first The few cases of deaths from this cause in infancy childhood and early adult life which already show a small difference in favor of women are not appreciable at the scale at which Figs 1 and 2 are drawn Mortality rates begin to diverge significantly at about the age of 30 male mortality rates rising sharply female mortality rates slowly After the mid fifties the curve of female mortality assumes an approximately parallel course with male mortality rates and this nearly parallel course is maintained into old age The

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Reprint requests to Mr S Seely 3 Truro Drive [illegible] Cheshire M33 5DF Great Britain

Books received

SESAP II Syllabus American College of Surgeons Chicago 1975 American College of Surgeons 461 pages

Self Assessment of Current Knowledge in Child Psychiatry By G P Sholevar M D Flushing N Y 1975 Medical Examination Publishing Co 276 pages

Dynamik Koronardurchblutung und Sauerstoffverbrauch des Normalen und Kranken Herzens By B E Strauer Basel 1975 S Karger AG 118 pages Price $16 75

Sarcoidosis A Clinical Approach By Om P Sharma M B B S F A C P Springfield Ill 1975 Charles C Thomas, Publisher 177 pages Price $17 50

Handbook of Tables for Mathematics Revised 4th edition Edited by Robert C Weast Ph D and Samuel M Selby Ph D Sc D Cleveland 1975 CRC Press Inc 1140 pages Price $29 95

Announcements

Hypertension symposia in Australia and New Zealand

Group tours to Australia and New Zealand February 20 to March 7 or March 14 are now being organized in association with attendance at the International Society of Hypertension meetings in Sydney Australia and the subsequent Symposium on the Genetic Hypertensive Rat in Dunedin New Zealand Persons interested in these meetings should contact the tour organizer Dr S W Hoobler University of Michigan Medical Center Ann Arbor Mich 48109 immediately

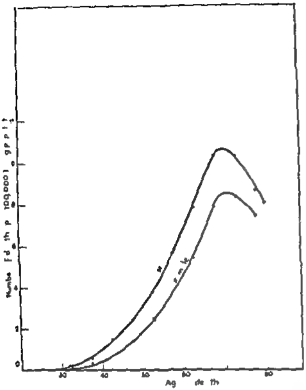

Fig 3 Ischemic heart disease Negro male and female mortality rates Louisiana and Mississippi 1969

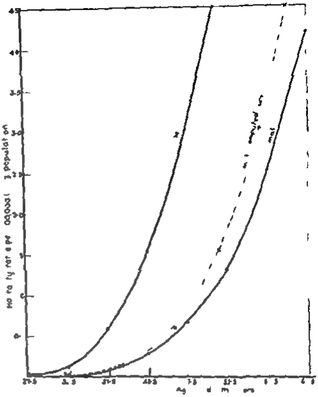

Fig 4 Ischemic heart disease White male and female mortality rates New York State 1969

difference between male and female resistivity to this disease is much less than in the case of ischemic heart disease Certain sections of these curves also follow a roughly parallel path but the distance separating them is of the order of only two years There is a similarly small difference between male and female resistivity to peripheral arteriosclerosis Women are notably resistant only to ischemic heart disease not to other forms of vascular disease

The original problem of the comparatively high resistance of women to ischemic heart disease appears to be associated with two additional problems One is to find the explanation of racial differences the other to explain why the factors which confer a degree of immunity to women from ischemic heart disease fail to apply to other forms of vascular disease The following sections of this paper will attempt to find answers to these questions But first it may be of interest to see whether existing hypotheses could adequately deal with the problems

Let us for instance consider stress This presumably acts through the intermedium of corticosteroids acting as depressants on some relevant aspect of reticuloendothelial activity e g the healing of ulcers often associated with atheroma or the fibrous reinforcing of vessel walls previously weakened by atheromatous plaques It seems however inconceivable that such depressant effects would apply to cerebral arteries but not to coronary arteries or vice versa The same argument also seems valid for the effects of smoking and alcohol consumption The writer suggests that these factors apply to all forms of vascular disease and their cumulative effect results in the comparatively small difference between male and female resistivity which is manifest in cerebrovascular disease Some factor which applies only to ischemic heart disease still has to be discovered

Etiological factors

As already mentioned in the introduction the hypothesis to be presented in this article presupposes some metabolic fault as the primary cause of atheroma Suggestions to this effect can be found in most modern textbooks of pathology but attempts to discover the nature of the hypothetical metabolic error have so far failed to

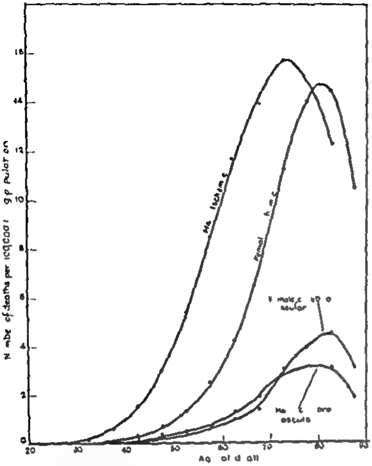

Fig 1 Ischemic heart disease and cerebrovascular disease Male and female mortality rates for white population New York State 1969

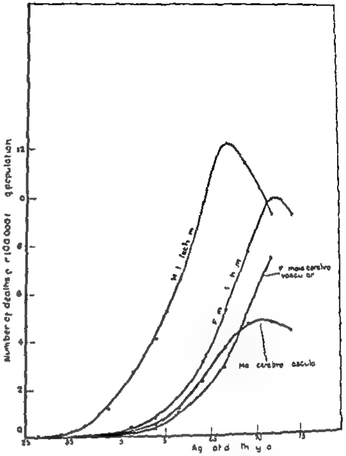

Fig 2 Ischemic heart disease and cerebrovascular disease Male and female mortality rates England and Wales 1971

difference in years separating these parallel sections of the curves—about 11 years in Fig 1 12 years in Fig 2—is the age difference at which parity of mortality rates is established between men and women Parity of mortality rates can be thought of as equal probability of dying from a given cause Thus the probability of a white female inhabitant of New York State dying of ischemic heart disease at the age of 50 is the same as her male counterpart dying at the age of 39, and the probability of a woman dying at 60 is the same as a man dying at the age of 49

The age difference separating the parallel sections of mortality curves is characteristic of various populations In white populations its usual range is 11 to 14 years As already pointed out, it is about 11 years in New York State 12 years in England and Wales The latter figure also applies for instance to West Germany When mortality rate from ischemic heart disease is low the difference in favor of women tends to be high Thus in the United States the difference of about 14 years corresponds to the lowest mortality rates from vascular disease in Alaska and New Mexico

The degree of difference between male and female resistivity to ischemic heart disease also appears to be a racial characteristic In American Negroes it is considerably less in Hawaiians somewhat more than in the white population No data are published in *Vital Statistics of the United States* for Negroes or Hawaiians as such only the white and non white populations are separated However the non white population of Louisiana and Mississippi are 99 per cent Negro their mortality rates from ischemic heart disease are shown in Fig 3 Data relating to the two states were combined to obtain mortality rates based on a reasonably large population

It is apparent from Fig 3 that the distance separating the parallel sections of the mortality curves is only 5 to 6 years The difference between Hawaiian men and women appears to be of the order of 17 years noting however, that the non white population of Hawaii is comparatively small, it includes other colored groups besides Hawaiians and the incidence of vascular disease in Hawaii is low

Turning to cerebrovascular disease it is evident from the mortality curves in Figs 1 and 2 that the

in female resistivity to heart disease. The amount of blood lost in menstrual hemorrhages is known to vary between wide limits: the quantity per menses can be ten times as high in some women as in others. It is therefore conceivable that there are considerable racial variations as well. Mortality rates from ischemic heart disease suggest that white women, at an average, lose more blood than Negro women but less than Hawaiian women.

The stumbling block is the difference between ischemic heart disease and cerebrovascular disease. If hemorrhages are capable of eliminating faulty metabolites, how is it possible that the reduction in the quantity of these metabolites affects only ischemic heart disease, not cerebrovascular disease?

The explanation offered is as follows. It must be assumed that cholesterol metabolism is subject to two faults, not one. In one case the result of the fault is uncontrolled precipitation. The other fault affects solubility in the opposite direction, with the result that the *withdrawal* of the affected particles from solution presents difficulties. In consequence the faulty metabolites tend to circulate uselessly in the blood stream, creating a health hazard, without any toxic qualities, with their mere presence. Hypercholesterolemia, or more generally, hyperlipoproteinemia, appears to be a disorder of this nature. Protein-bound calcium salts circulating in the blood stream, for which no function is known to exist, may be another example.

The only method of removing faulty metabolites of this type from the blood appears to be their capture by macrophages. In serious cases of hyperlipoproteinemia large multinucleate leucocytes, often termed foam cells or lipophages, proliferate rapidly and can be seen laden with lipids in the blood. The presumable destination of these cells is the liver, to be voided via the gall bladder into the intestine, but as the gall bladder can cope with only a limited quantity, congestion in the spleen and liver may occur, where masses of lipophages may cause splenomegaly and hepatomegaly. The often heard suggestion that lipophages serve for the *storage* of lipids seems of doubtful validity. Normal lipids, sometimes in immense quantities, are stored in fat depots; there is no reason to believe that macrophages are needed to remove them from the blood.

It is not yet certainly determined, but perhaps some of these lipid-laden macrophages become trapped in high pressure capillaries to be eventually released to find their way into the intima of some large and medium size arteries, where the cells die and release their load of lipids. Once deposited, these faulty metabolites cannot be removed and after decades of accumulation they may give rise to the formation of atheromatous plaques.

In the other type of disorder, in which presumably much smaller quantities are involved, true precipitation of cholesterol and other lipids is thought to occur on vessel walls which macrophages are unable to remove. The precipitates may cause necrosis of the underlying epithelial cells by depriving them of oxygen and nutrients. The precipitates are finally overgrown by newly formed epithelium. In other words, the classic encrustation theory is thought to be valid in one type of disorder, the imbibition theory in the other. It is not suggested that precipitation is restricted entirely to cerebral arteries and the other type of disorder to the aorta and coronary arteries, but they appear to show a preference for these respective locations. The writer can offer no explanation for these preferences.

A hemorrhage is effective in removing an appreciable quantity of only that type of faulty metabolite which tends to stay suspended in the plasma. The type which tends to form precipitates quickly disappears from the blood, so that a hemorrhage is ineffective in disposing of an appreciable quantity of it. This is the suggested reason why menstruation gives women a measure of protection against one type of disorder and not against the other. Faulty cholesterol metabolism is *not* thought to be involved in peripheral arteriosclerosis.

Some quantitative aspects of the advanced hypothesis

Assuming that the advanced hypothesis is acceptable in principle, it needs to be demonstrated that it does not involve quantitative absurdities, notably that it does not presuppose the removal of far too large quantities of faulty metabolites in far too small quantities of menstrual blood. A rough check can be made as follows.

It is necessary to form a rough estimate of the weight of the fatty material of atheromatous plaques at death. For want of more accurate information it is assumed that this is of the order of a few grams, let us say, *30 Gm*. In the average

materialize Hence it may be of interest to note some remarkable similarities between atheroma and gout, a disorder well understood to be of metabolic origin The basic similarity between them is that in both cases the uncontrolled precipitation of insoluble or sparsely soluble substances may be involved

One of the remarkable features of animal life is the apparent ease with which insoluble or sparsely soluble materials like fats cholesterol, calcium salts, uric acid and its salts are transported in the plasma The ease is more apparent than real the hazards of the process are demonstrated by occasional instances of uncontrolled precipitation in locations where the precipitates endanger the life of the animal Calculi of urates in the kidney, cholesterol in the gall bladder and calcium salts in various ducted glands are the obvious examples

Another point of similarity between atheroma and gout is a strong preference for certain locations The high incidence of atheroma in the coronary arteries is matched by the nearly invariable first appearance of gout in the metatarsophalangeal joint of the big toe Similarly, urate containing tophi on the pinnae of the ears are matched by cholesterol containing xanthelasma on the eyelids

The similarity most relevant to the present discussion is the virtual immunity of premenopausal women from gout

The reason for the study of these similarities is that gout is a simpler and better understood disorder than atheroma The appearance of uric acid crystals in joints seems nothing more than the precipitation of crystalloids from solution when a critical level of concentration is exceeded Such a comparatively simple disorder may assist in the understanding of a related complex phenomenon by analogy or contrast For instance the frequent appearance of gout in the small joints of toes and fingers the pinnae of the ears etc may be explained by the comparatively low temperature of such locations Precipitation of crystalloids from solution is known to be accelerated by low temperature It is not impossible that atheroma in contrast seeks out locations of comparatively high temperature The heart, among its other functions, is a permanently active heat generator

Let us consider the virtual immunity of premenopausal women from gout The relevant facts are that the normal concentration of uric acid in the plasma of men is of the order of 7 mg per 100 ml, which is nearly the limit of tolerance, precipitation tending to occur at 8 mg In women the normal concentration is about 1 mg per 100 ml less before the menopause, the small difference being apparently sufficient to provide an adequate margin of safety After menopause uric acid concentration in women also begins to approach and occasionally exceed the limit of tolerance

The reason for the lower concentration in the plasma of women cannot lie in the metabolic process The endproduct of purine metabolism is uric acid, regardless of sex The difference therefore, must be either in diet or in the excretion of uric acid As it is improbable that women significantly change their dietary habits after menopause the question remains whether menopause can be assumed to bring a significant change in excretion

The suggested answer is that menstrual hemorrhages may play a part in the elimination of uric acid during the reproductive part of a woman s life, relieving the kidneys from a part of their load An average woman loses approximately 1 per cent of the total blood volume per menses, about 10 per cent per year The lost blood contains its normal quota of uric acid, the nascent blood produced to replace it is clean so that in this sense and to this extent a hemorrhage no matter how caused, has a cleansing effect After menopause the kidneys of men and women function under the same conditions and have equal difficulties in keeping uric acid concentration below the critical level

On this analogy the possibility exists that menstrual blood loss may also be responsible for the comparatively high resistance of women to ischemic heart disease The blood lost in a hemorrhage contains not only uric acid but a proportionate fraction of any noxious substance carried in the plasma Consequently menstruation relieves not only the kidneys from some of their load but all organs which excrete sparsely soluble waste products Since the path of such excretory processes is marked by the occasional formation of calculi it can be surmised that the organs in question are the liver in case of cholesterol and the salivary glands, pancreas liver kidney, and prostate in case of insoluble calcium salts

A point in favor of this hypothesis is that it is consistent with the existence of racial differences

Preclinical cardiomyopathy in chronic alcoholics: A sex difference

Chia F. Wu, M.D.
Maraboyina Sudhakar, M.D.
Ghazanfar Jaferi, M.D.
S. Sultan Ahmed, M.D.
Timothy J. Regan, M.D.
Newark, N. J.

Clinical descriptions of cardiomyopathy in alcoholics have consistently indicated a predominant male distribution. Although this may be related to a difference in the sex incidence of alcoholism, a variation in the myocardial response to long-term ethanol use needs to be considered.

While a preclinical abnormality of cardiac function has been described in male alcoholics,[2-6] female subjects were rarely studied and the question of sex difference has not been examined. We have chosen this phase of the myocardial response to chronic ethanol use to examine this issue. Male and female alcoholics with a similar history in terms of duration and intensity were selected. In addition, a group with similar pathology of the liver manifested as cirrhosis was compared. Noninvasive studies of left ventricular function and conduction were performed.

Methods

Studies were performed on 36 patients admitted to the hospital for a variety of alcohol-related diseases. They were all chronic users of ethanol. Quantitation of history was approximate and was also obtained from relatives or friends in most instances. The average duration was 15 years and recent consumption of whiskey ranged from 8 to 32 oz. per day. Alcoholic subjects with signs and symptoms indicating presence of heart disease, hypertension, diabetes mellitus, pulmonary disease, and obesity were excluded from this study. The subjects were otherwise consecutive in that none were excluded who gave consent.

Conventional 12 lead electrocardiograms (ECG) and chest roentgenograms were normal in all the subjects. A total of 22 males and 14 females were investigated. Nineteen were found to have alcoholic cirrhosis confirmed by liver biopsy. Patients presented with delirium tremens or mild withdrawal symptoms, acute alcoholic gastritis, acute or chronic pancreatitis, etc. All subjects were studied after acute symptoms and signs had dissipated and were abstinent from alcoholic beverages for an average of 12 days (range 4 to 60 days). Blood pressure was measured at the time of study and blood hematocrit, electrolytes, and liver function tests were obtained at or near the time of study. Twenty-two volunteers without heart disease who were known to be nonalcoholic served as a control group. All studies were done between 8:00 A.M. and 12:00 noon in the postabsorptive phase and the supine position.

The systolic time intervals were measured as described by Weissler and associates[7] from simultaneous ECG, phonocardiogram, and external carotid pulse tracings. These were recorded on an Electronics for Medicine oscillographic recorder at a paper speed of 100 *mm. per second* and time markers of 0.02 sec. The total electromechanical systole (QS$_2$) was measured from the beginning of the QRS complex to the first rapid deflection of the second heart sound. The left

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From the Department of Medicine, College of Medicine and Dentistry of New Jersey, New Jersey Medical School and Martland Hospital Unit, Newark, N. J.

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Reprint requests: Timothy J. Regan, M.D., New Jersey Medical School, 100 Bergen St., Newark, N. J. 07103.

case of death caused by atheroma this represents the accumulation of 60 or more years so that the accumulation of faulty metabolites is assumed to proceed at the rate of 0 5 Gm per year

From the point of view of the accumulation of faulty metabolites a woman s age at the onset of menopause is about 12 years less than that of her male contemporaries Of these, perhaps two years can be attributed to less smoking, more placid life, etc the advanced hypothesis, therefore, is equivalent to saying that menstrual hemorrhages of 35 years can eliminate 10 years net accumulation of faulty metabolites namely 5 Gm in terms of the example The average quantity of blood lost by a woman is known to be of the order of 35 ml per menses In 35 years at this rate the lost blood amounts to about 16 L or three complete changes of blood This volume of blood would eliminate 5 Gm of atherogenic metabolites if its metabolite content were 33 mg per 100 ml The normal cholesterol content of blood is of the order of 120 mg per 100 ml reaching 1000 mg in serious cases of hypercholesterolemia hence the assumed concentration of faulty metabolites does not appear excessive

Lastly we will attempt to show that the advanced hypothesis can correlate male and female mortality rates from ischemic heart disease to a reasonable degree of accuracy Let us assume that men and women are at equal risk of dying of ischemic heart disease when their accumulation of atherogenic substances is equal Before the menarche and after the menopause women are assumed to accumulate these substances at the same rate as men but in the interim 35 years they do so at a lower rate by virtue of menstruation White women appear to gain an advantage of 11 to 14 years by the onset of menopause in comparison with men The difference is assumed to be multicausal two years of the gain are attributed to factors other than menstruation on the analogy of cerebrovascular disease Menstrual hemorrhages are assumed to account for the remaining 9 to 12 years This means that the net accumulation of atherogenic substances in years of menstruation must be assumed to be reduced by 25 7 to 34 per cent Taking the lower figure a woman of 40 for example, would accumulate the same amount of atherogens as a man in 14 + 0 743 × 26 = 33 3 years, hence according to hypothesis the probability of her dying of ischemic heart disease at the age of 40 is the same as that of a man at the age of 33 3

In general terms, taking the age of menarche and menopause at 14 and 49, and denoting the actual age of a man by the symbol A_m and the equivalent age of a woman by the symbol A_f then, before the menopause

$$A_m = 14 + 0\,743\,(A_f - 14)$$
$$A_f = 1\,35 A_m - 4\,84$$

After menopause

$$A_m = 14 + 0\,743 \times 35 + (A_f - 49)$$
$$A_f = A_m + 9$$

With the aid of these formulas it is possible to take points from a male mortality curve and calculate corresponding points on a computed female mortality curve The object is to see how the computed curve compares with the actual rates of female mortality

Fig 4 shows a part of Fig 1 on a larger scale Actual male and female mortality rates from ischemic heart disease are shown in full lines a computed curve of female mortality rates is shown in a broken line This seems to approximate the shape of the actual curve of female mortality rates to a reasonable degree of accuracy The gap between the actual and computed mortality curve represents the approximate gain of two years attributed to factors other than menstruation

Conclusion

Apart from the theoretical implications of the advanced hypothesis it is suggested that venesection should be reconsidered as a possible therapeutical measure Venesection up to the beginning of the nineteenth century was perhaps the most over used and abused form of therapy in medical history which rightly fell in disrepute with the advance of science Nevertheless in some cases it may be possible to employ it with advantage Hyperlipoproteinemia and gout may be such disorders particularly cases when the patient suffers from both

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Table II Comparison of systolic time intervals in male and female alcoholics

	Normal		All alcoholics			Cirrhosis		
	Male	*Female*	*Male*	*Female*	*P*	*Male*	*Female*	*P*
Number	11	11	2?	14		9	10	
Age	34.4 ± ?.6	33.? ± 3.0	39.4 ± 1.8	35.7 ± 2.1	NS	37.0 ± 3.5	35.0 ± 2.3	NS
Blood pressure								
S	123.5 ± 3.3	111.1 ± 5.1	126.8 ± 3.9	116.9 ± 4.0	NS	123.5 ± 4.6	117.3 ± 5.5	NS
D	79.8 ± 2.0	?5.1 ± 3.0	81.1 ± 2.?	70.0 ± 2.8		81.1 ± 3.7	?0.4 ± 3.8	NS
HR/min	64.7 ± 2.4	68.5 ± 2.0	81.6 ± 2.1†	81.2 ± 4.0‡	NS	85.3 ± 4.0†	79.5 ± 4.5‡	NS
PEP/LVET	0.316 ± 0.007	0.310 ± 0.01	0.419 ± 0.0?†	0.3?2 ± 0.015	†	0.400 ± 0.023	0.3?1 ± 0.017	‡
PEP (msec)	9?.4 ± 3.6	92.5 ± 3.1	107.0 ± 4.1‡	90.0 ± 4.4	‡	10?.3 ± 6.0	91.4 ± 5.0	NS
PEPI (msec)	116.0 ± 3.1	120.0 ± 3.0	139.6 ± 4.0†	12?.4 ± 3.6		136.4 ± 6.1‡	123.2 ± 4.4	NS
LVETI (msec)	401.5 ± 5.8	409.1 ± 5.5	397.2 ± 4.8	410.6 ± 4.5	‡	401.3 ± 4.1	413.0 ± 4.6	NS
QS_2I (msec)	519.7 ± 8.2	531.1 ± 6.8	536.5 ± 5.5	533.3 ± 5.0	NS	537.6 ± 8.5	53?.4 ± 5.4	NS

Superscript symbols indicate statistical significance compared to normals of the corresponding sex * = P < 0.005 † = P < 0.001 ‡ = P < 0.05 unlabelled not significant.
Column heading P represents a comparison between males and females of the respective groups

Table III History and laboratory data in cirrhotics

	Duration of alcohol (yr.)	Estimated quantity (oz./day)	Serum							
			Hct	*K*	*SGOT*	*SGPT*	*Alk P*	*Bilirubin*	*Albumin*	*Prothrombin time*
Males	15.1 ± 1.4	16.0 ± 0	35.8 ± 2.0	4.5 ± 0.2	85.8 ± 22.9	31.0 ± 5.2	53.7 ± 10.3	2.8 ± 0.9	3.5 ± 0.2	13.8 ± 0.9
Females	14.3 ± 1.1	13.8 ± 1.9	30.9 ± 1.7	3.4 ± 0.2	142.0 ± 2?.0	34.6 ± 6.6	?3.3 ± 7.6	6.3 ± 1.9	?.9 ± 0.3	16.4 ± 0.3
P	NS	NS	NS	< 0.05	NS	NS	NS	NS	NS	< 0.2

Whereas the normal males and females showed no significant difference in these intervals male alcoholics had a more prolonged PEP/LVET ($P < 0.001$) PEPI ($P < 0.005$) PEP ($P < 0.05$) and shorter LVETI ($P < 0.05$) than the female alcoholics The slightly prolonged PEP/LVET and PEPI in the female alcoholics was not statistically different from the normal females

This difference between sexes was further examined in a more homogenous group of patients with biopsy proved cirrhosis of the liver The number of subjects age duration and quantity of alcohol intake abnormality of liver function and degree of anemia were comparable (Table III) Systolic and diastolic arterial pressures and heart rate were not *significantly* different In the male cirrhotics PEP PEPI and the PEP/LVET ratio were significantly prolonged compared to normal males whereas female cirrhotics did not differ significantly from *normal females* The PEP/LVET ratio was significantly higher in the male vs female cirrhotics Comparison of male and female cirrhotics showed *no* difference in PEPI LVETI and QS_2I, but a tendency for greater abnormality was *noted in* the former

High fidelity ECG studies Table IV presents the results of the high speed high fidelity ECG s recorded in 31 alcoholics compared with 10 normals A significant prolongation of the mean QRS duration to 89.2 msec was seen in the total alcoholic group Heart rate corrected PRc and QRc were also *significantly* prolonged ($P < 0.001$) QRS prolongation was present in the total alcoholic group *and in* the male alcoholic with and without cirrhosis There was no significant QRS prolongation in the female with or without cirrhosis

The number of QRS notches *as well* as notches and slurs combined from 12 leads were signifi

Table I Systolic time intervals in chronic alcoholics

	Normals		Alcoholics					
			Total		Cirrhosis		Noncirrhosis	
Number	22		36		19		17	
Age	34.0	± 1.9	38.0	± 1.4	35.9	± 2.0	40.3	± 1.9
Blood pressure								
S	117.3	± 3.3	123.0	± 2.[illegible]	120.3	± 3.6	126.1	± 4.8
D	77.5	± 1.8	76.8	± 1.[illegible]	75.5	± 2.9	78.3	± 2.6
HR/min	66.6	± 1.6	81.5	± 2.0†	82.3	± 3.1†	80.6	± 2.6‡
PEP/LVET	0.313	± 0.006	0.391	± 0.016†	0.359	± 0.017‡	0.406	± 0.027†
PEP (msec)	92.5	± 2.3	100.4	± 3.3	96.6	± 3.9	104.6	± 5.4
PEPI (msec)	119.0	± 2.1	132.9	± 3.1†	129.5	± 3.9	136.8	± 4.9‡
LVETI (msec)	405.3	± 4.0	402.4	± 3.5	407.5	± 3.3	396.8	± 6.3
QS$_2$I (msec)	525.4	± 5.4	535.2	± 3.8	537.0	± 4.8	533.2	± 6.3

*P<0.05 compared with normal group
†P<0.001 compared with normal group
‡P<0.005 compared with normal group

ventricular ejection time (LVET) was measured from the onset of the rapid upstroke of the carotid pulse to the nadir of the incisural notch. The preejection period (PEP) was derived from QS$_2$ minus LVET and the PEP/LVET ratio calculated. All intervals represent the mean of 10 consecutive beats, each derived to the nearest 5 msec. The indices QS$_2$I, PEPI and LVETI were obtained by applying normal regression equations for male and female.[8,9] Heart rate (HR) was obtained by multiplying the reciprocal of the mean RR interval by 60.

High fidelity ECG's were obtained in 31 alcoholic patients with and without cirrhosis (18 males, 13 females) and 10 normal subjects at a paper speed of 200 mm per second and time markers of 1 second.[9,10] The amplitude of the QRS complexes was set to about half of the paper width and the frequency response was set from 0.1 to 2000 cycles per second. Standard scaler limb and precordial leads were used in all recordings. Duration of the PR, QRS and QT intervals were obtained from this expanded time scale ECG. Notches and slurs in the QRS complexes were identified as described;[9,10] slurs are defined as changes of slope without changes of sign, notches are defined as a departure in both slope and sign. Directional changes of the QRS complexes such as the nadir of Q and S waves or peak of R waves were *not included in notch counts*. Number of notches and number of notches and slurs were independently summed from the 12 leads. To be included in the count, the notches and slurs were required to be present in a series of five or more beats. In addition, the presence of Q waves in Leads I, V$_5$ and V$_6$ was noted.[11] Statistical analyses were performed by using the nonpaired Student t test.

Regression equations
Male
QS$_2$I = QS$_2$ + 2.1 × HR
LVETI = LVET + 1.7 × HR
PEPI = PEP + 0.4 × HR
Female
QS$_2$I = QS$_2$ + 2.0 × HR
LVETI = LVET + 1.6 × HR
PEPI = PEP + 0.4 × HR

Results

Table I summarizes the STI results (mean ± standard error of mean) for the total noncardiac alcoholics that were studied as well as the subgroups. The ages from each group were comparable. Systolic and diastolic arterial pressures were not significantly different from the control group, but a significantly higher heart rate in alcoholic subjects was found. The PEP/LVET ratio was significantly higher in the alcoholic ($P < 0.001$), cirrhotic ($P < 0.005$) and noncirrhotic ($P < 0.001$) groups. There was a *significant prolongation* of the PEPI as well as PEP without significant changes in LVETI and QS$_2$I. The subgroup with liver cirrhosis tended to show a lesser degree of abnormality but was not statistically different from the noncirrhotic group.

Comparison of males and females. In Table II a comparison of the systolic time intervals between alcoholic males and females is indicated

observations in three nonalcoholic patients with moderate anemia at hematocrit levels between 25 and 30 per cent No significant difference in systolic time intervals compared to normals was found More severe chronic anemia is apparently required to evoke hemodynamic change and these may be evidenced as enhanced rather than reduced ventricular function [7]

The high fidelity ECG also showed abnormalities which were not readily observed on the conventional ECG The PRc QRS and QTc were prolonged in the total alcoholic group and the septal Q was frequently absent Enhanced notching and slurs in the QRS are consistent with a primary myocardial disease process [9] The conduction changes appeared unlikely to be due to increased ventricular mass since heart size was within normal limits by clinical examination chest x ray and ECG Prolonged conduction has also been observed in the well nourished chronic ethanolic animals without cardiac hypertrophy

These conduction parameters were also significantly prolonged in the 18 alcoholic males Although a similar relationship was present in the subgroup with cirrhosis there were insufficient males to show a statistical difference in PRc QRS was not significantly altered in the 13 females or the subgroup with cirrhosis The consistent prolongation of PRc and QTc in females may be attributable to either the observed hypokalemia or chronic ethanol ingestion If due to the latter this would represent an apparent greater sensitivity of the female to the effects of ethanol on bioelectric properties of myocardium than on mechanical function

Summary

Alcoholic subjects differ in the incidence of cardiomyopathy Of potential variables sex may be important since few females are seen with cardiomyopathy even adjusting for the lower incidence of alcoholism To examine this question noninvasive systolic time intervals were measured in 22 males and 14 females of similar age heart rate and arterial pressure without clinical evidence of heart disease or hypertrophy Duration and intensity of ethanol intake and the interval from last drinking episode were apparently equivalent In male alcoholics the left ventricular preejection period and ejection time (PEP/LVET) ratio of 0.410 ± 0.020 was significantly higher than in the 11 normal males (0.316 ± 0.007) ($P < 0.001$) In female alcoholics the ratio was 0.322 ± 0.015 compared to 0.310 ± 0.01 for 11 normal females and was significantly less than in the male patients ($P \pm 0.001$) In addition prolonged intraventricular conduction by high frequency ECG was more prevalent in the male group

To further ensure equivalency of alcoholism patients with biopsy proved cirrhosis were selected In nine males PEP/LVET was significantly higher than in the 10 females Thus abnormal myocardial function was evident in males but not in females suggesting that sex is a determinant of the toxic effects of ethanol on myocardium

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Table IV Conduction time in chronic alcoholics

	Normals	All alcoholics	Alcoholics		Cirrhosis	
			Male	Female	Male	Female
Number	10	31	18	13	5	11
Age	38.2 ± 2.9	36.9 ± 1.6	37.7 ± 1.4	35.7 ± 2.0	36.4 ± 2.3	34.0 ± 1.[illegible]
HR/min	62.5 ± 2.5	84.2 ± 2.6	82.6 ± 3.0	86.4 ± 4.8*	96.8 ± 7.4†	84.1 ± 5.3†
PR	152.0 ± 8.0	159.2 ± 4.6	160.1 ± 6.9	158.0 ± 5.8	146.6 ± 12.2	157.8 ± 6.8
PR	153.3 ± 5.6	186.3 ± 5.1*	184.3 ± 6.0†	187.9 ± 9.0†	174.3 ± 11.7	185.0 ± 10.4‡
QT	371.1 ± 7.5	377.6 ± 4.9	370.9 ± 5.3	397.0 ± 8.6	363.0 ± 9.0	389.2 ± 8.1
QT	376.9 ± 5.6	442.9 ± 6.6	431.7 ± 5.6	458.5 ± 12.9	431.6 ± 9.9	453.5 ± 11.0
QRS	78.9 ± 2.2	89.2 ± 1.8	92.0 ± 2.2*	85.3 ± 2.8	89.8 ± 3.1‡	86.5 ± 3.0
Number of notches and slurs	10.[illegible] ± 1.3	15.4 ± 1.2†	16.5 ± 1.9†	13.9 ± 1.3	18.4 ± 3.8	14.8 ± 1.4‡
Notches only	4.1 ± 0.6	8.8 ± 0.8	9.5 ± 1.0*	7.7 ± 1.2†	10.2 ± 1.8†	8.3 ± 1.3†
Absent septal Q	0	9 (29%)	6 (33%)	3 (23%)	1 (20%)	3 (27%)

* = P < 0.001 all statistical comparisons are with the normal group
† = P < 0.01
‡ = P [illegible] 0.0[illegible]
All intervals in msec

cantly more numerous in the total group of alcoholics. Although there was a tendency for greater abnormality of these parameters in the males, the numbers were apparently not sufficient to demonstrate a difference from female alcoholics. In nine of these 31 patients (29 per cent) the septal Q was absent in Leads I, V_5 and V_6 but the numbers were insufficient to consider a sex difference. In contrast, the septal Q was present in all 10 normal subjects.

Discussion

Demonstration of abnormal left ventricular function in alcoholic subjects without clinical evidence of heart involvement has been reported in several studies.[1-3] Our data in the total alcoholic group are in accord with these observations. The most significant alterations of the systolic time intervals were found in the prolonged PEP and PEPI and increased PEP/LVET. This may be attributed to a depressed contractile state[12] or diminished compliance of the left ventricle. The latter interpretation is supported by findings in a canine model of chronic ethanolism. Enhanced diastolic stiffness of the ventricle was associated with glycoprotein accumulation in the interstitium of an experimental model[13] and a similar histochemical abnormality has been seen in noncardiac alcoholics with cirrhosis.[14]

This study is in accord with the general view that congestive cardiomyopathy is infrequent in patients with cirrhosis[1] but a preclinical abnormality would appear to be common in male cirrhotics.[3, 4] The normal time intervals in females was unlikely to be due to lesser intensity or duration of alcoholism since the females had cirrhosis of equal or greater severity as judged by prothrombin times. This absence of a functional abnormality in the female suggests that the sex hormones are a determinant in the development of the preclinical entity and presumably the clinical cardiomyopathy. The functional abnormalities in the males is not likely to be due to coronary artery disease for several reasons. The normals were of similar age and alcoholics with cirrhosis appear to have less atherosclerosis at postmortem than the nonalcoholic population.[15] Moreover, patients with angina without cardiac decompensation frequently have normal systolic time intervals.[16]

Although some of the alcoholic patients had clinical evidence of mild malnutrition, particularly in the female group, the normal systolic intervals in the latter suggest that malnutrition was not a determinant of the abnormal systolic time intervals. In addition, the degree of anemia in these patients was not severe enough to cause hemodynamic alterations. This is supported by

Atrioventricular conduction patterns in patients with paroxysmal supraventricular tachycardia

Joe K Bissett MD
Neil de Soyza MBBS
James J Kane MD
Marvin L Murphy MD
Little Rock Ark

Electrophysiologic studies in the canine heart have demonstrated a marked increase in the A V nodal delay of early premature atrial stimuli suggesting the possibility of dual A V nodal pathways. This conduction pattern is also demonstrable in the human heart by the extrastimulus technique when an abrupt increase in A V nodal delay is produced by a minimal decrease in the test atrial stimulus[1,2] Further studies have suggested a relationship between these properties of the atrioventricular conduction system and the occurrence of paroxysmal A V nodal re entrant tachycardia (PSVT) in patients with normal and short PR intervals[3] The incidence of conduction patterns suggesting dual A V nodal pathways in patients with and without PSVT is unknown. Recent reports have suggested that this type of A V conduction is common and may be seen in patients without a history of PSVT[4]

The purpose of this study is to report the incidence of dual A V nodal pathways in 148 patients with varying PR intervals studied at similar basic cycle lengths to minimize the effects of rate on A V conduction and permit comparison. The results establish a strong association between this conduction pattern and PSVT. The occurrence of dual A V nodal pathways was found to be uncommon in patients without PSVT and did not occur with increased frequency in patients with short or long PR intervals

Methods

After informed consent had been obtained the properties of the A V conduction system were evaluated in 13 patients with documented paroxysmal supraventricular tachycardia (PSVT) (mean age 53 ± 8 years) and 135 patients without a history of paroxysmal tachycardia. The patients without a history of tachycardia were further subdivided into those with normal PR intervals (106 patients mean age 49 ± 8 years) PR intervals of 120 msec or less (12 patients mean age, 55 ± 7 years) and PR intervals of 200 msec or greater (17 patients mean age, 54 ± 10 years) Three patients in the group with PSVT had PR intervals of 200 msec or greater the remainder had normal PR intervals

Right heart catheterization was performed in all subjects in the supine postabsorptive state. His bundle electrograms were obtained by standard catheter technique and the refractory periods of the A V conduction system were measured by the extrastimulus method[5] The atria were paced at a basic drive rate of 660 to 720 msec by a Tektronix 2600 series stimulator and a premature atrial stimulus was introduced after every tenth drive beat. The coupling interval of the premature atrial stimulus was then decreased in intervals of 5 to 10 msec until the refractory period of the atrium was reached. Standard electrocardiographic (ECG) Leads I II III and V_1 were recorded simultaneously with the His bundle electrogram and high atrial electrogram on a multichannel oscilloscopic recorder (Electronics for Medicine)

From the Veterans Administration Hospital, Department of Medicine and University of Arkansas School of Medicine Little Rock Ark

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Reprint requests Joe K Bissett, MD Department of Medicine Veterans Administration Hospital, 300 E. Roosevelt Rd. Little Rock, Ark. 72206.

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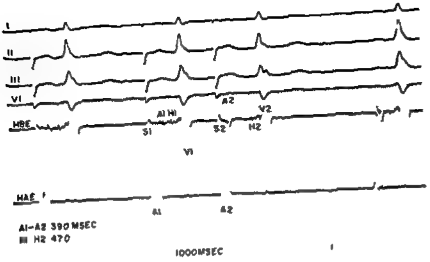

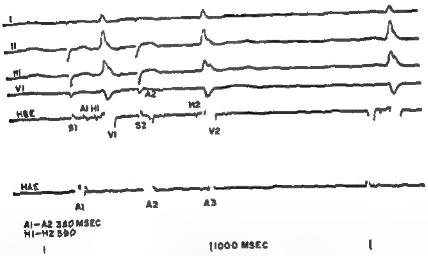

Fig 2 His bundle recordings in a second patient with PSVT and dual A V nodal pathways Standard ECG Leads I II III and V are shown with the His bundle electrogram (HBE) and high atrial electrogram (HAE) In the top panel an A1 A2 interval of 390 msec is associated with an H1 H2 interval of 470 msec Reduction in the A1 A2 interval to 380 msec (bottom panel) is accompanied by a large increase in A V nodal delay with an H1 H2 interval of 590 msec and production of an atrial echo (A3)

Table I Results of conduction studies

	AH (msec)	*HV* (msec)	*Functional refractory period A V node* (msec)	*Patients with dual A V nodal pathways*	*Patients without dual pathways*
Group 1 Patients with PSVT	110 ± 32	50 ± 8	457 ± 70	7	6
Group 2 Normal PR intervals without PSVT	87 ± 17	48 ± 11	418 ± 42	8	98
Group 3 Short PR intervals without PSVT	64 ± 9	45 ± 9	3.9 ± 36	0	12
Group 4 PR intervals greater than 200 msec without PSVT	15? ± 45	57 ± 10	469 ± 57	1	16

$P < 0.01$ when compared with group 1

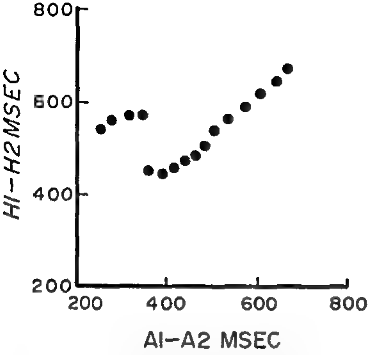

Fig 1 Results of conduction studies in a patient with documented paroxysmal supraventricular tachycardia The interval between premature atrial stimuli (A1 A2 interval) is shown on the X axis and the resulting interval between His bundle depolarizations (H1 H2) is shown on the Y axis As the A1 A2 interval is reduced below 350 msec there was a marked increase in A V nodal delay with a significant increase in the H1 H2 interval The sudden alteration of A V nodal delay with a change in the slope of the conduction curve suggests the presence of dual A V nodal pathways

Definitions

The letters A H, and V refer to depolarizations of the atrium His bundle and ventricle respectively The numeral 1 refers to depolarization produced by the drive atrial beat and the numeral 2 refers to depolarizations produced by the premature atrial stimulus In each patient the response of the A V node to premature atrial stimulation was characterized by plotting H1 H2 intervals versus A1 A2 or coupling intervals (Figs 1, 2, and 3) The presence of dual A V nodal pathways was defined by the method of Rosen and associates[4] when a minimal decrease in the A1 A2 interval was accompanied by a marked increase in A V nodal delay with a subsequent change in slope of the conduction delay plot (Fig 1) [4]

The functional refractory period of the A V node was defined as the minimum interval between two successive His bundle responses both propagated from the atrium[6] The A H interval was used as an approximation of A V nodal conduction time and the H V interval was used as a measure of His Purkinje delay

Administration of Inderal

In 27 patients, four with PSVT and 23 without arrhythmia (17 with normal PR intervals and four with PR intervals of 120 msec or less) the effect of Inderal on the pattern of A V conduction was measured In these patients conduction studies were repeated 5 to 10 minutes after the administration of 0 1 mg per kilogram of Inderal intravenously

Results

Conduction studies were completed in all 148 patients without difficulty The results of these studies are shown in Table I The incidence of dual conduction pathways was significantly increased in patients with PSVT when compared with the other groups ($P < 0.01$ by chi square test) Dual A V nodal pathways were found in seven of 13 patients with PSVT eight of 106 patients with normal PR intervals without PSVT, none of 12 patients with short PR intervals without PSVT and one of 17 patients with PR intervals of 200 msec or greater without PSVT An example of the type of response seen in patients with PSVT is shown in Figs 1 and 2 Five patients in the group with PSVT developed atrial echoes during premature atrial stimulation (Fig 2) No patient in the other groups developed echo beats during premature atrial stimulation

The AH interval in patients with PSVT was significantly longer than the AH intervals seen in patients without PSVT and patients with short PR intervals Although the significance of this finding is unknown, it may simply reflect the fact that three patients in the group with PSVT had PR intervals of 200 msec or greater with AH intervals of 130 msec or greater When the functional refractory period of the A V node was compared in the four groups patients with PR intervals less than 200 msec were found to have a significant reduction when compared with patients with PSVT This phenomenon may represent an intrinsic property of the A V node in patients with short PR intervals [7]

Four of the six patients with paroxysmal atrial tachycardia who did not have dual conduction pathways were restudied after 0 1 mg per kilogram of propranolol was given intravenously Two of these patients then developed conduction patterns consistent with dual A V nodal pathways (Fig 3) Twenty three patients with normal conduction patterns without a history of parox

106 patients with normal PR intervals none of 12 patients with short PR intervals, and one of 17 patients with PR intervals of 200 msec or greater The incidence of dual A V nodal pathways was significantly greater ($P < 0.01$) in patients with PSVT when compared with all other groups In two of four patients with PSVT propranolol was found to unmask evidence of dual pathways no evidence of dual pathways was produced by propranolol in 23 patients without PSVT

The data show that the pattern of dual A V nodal pathways is common only in patients with PSVT and is significantly less frequent in patients without PSVT regardless of the presence of short or long PR intervals

The results of this study establish a strong association between this conduction pattern and the occurrence of PSVT in man

The authors gratefully acknowledge the secretarial assistance of Miss Lisa Goodwin

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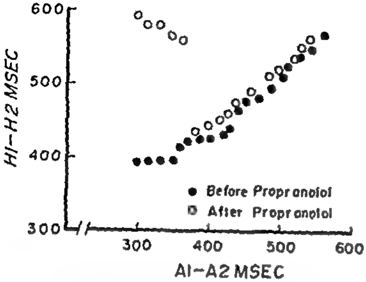

Fig 3 Demonstration of dual A V nodal pathways after propranolol Baseline conduction studies (closed circles) in a patient with documented PSVT did not show evidence of dual pathways When conduction studies were repeated 10 minutes after the administration of 0 1 mg per kilogram of propranolol the curve relating coupling interval (A1 A2) to A V nodal delay (H1 H2) showed a sudden break with a change in slope suggesting dual A V nodal pathways

ysmal atrial tachycardia were studied in a similar manner, no patient in this group developed an alteration suggestive of dual pathways

Discussion

This study demonstrates the frequency of conduction patterns suggesting dual A V nodal pathways in patients with and without PSVT While seven of the 13 patients with PSVT had evidence of dual A V nodal pathways only eight of 106 patients without a similar history had this conduction pattern ($P < 0.01$) In addition, there did not appear to be a significant increase in the incidence of dual pathways in patients with short PR intervals or A V nodal dysfunction in the absence of documented PSVT

The anatomic correlation of this conduction pattern is unclear Although pathologic studies have demonstrated fibers which appear to bypass a portion of the A V node,[8] their significance in human conduction is unknown The occurrence of separate conduction pathways may also be due to longitudinal dissociation within the A V node within a region where lateral propagation does not occur[9]

It is clear that not all patients with documented episodes of supraventricular tachycardia due to re entry have conduction patterns suggestive of dual pathways[4 10] These patients may have re entry of the premature impulse into the normal pathway from an area of depressed conduction The critical AH interval required for initiation of PSVT might represent the delay necessary for reflection into the normal pathway as previously suggested[2] These mechanisms are not mutually exclusive and have in common the occurrence of differential conduction in a critical area of the A V conduction system It is also evident that the evidence for dual pathways may be affected by autonomic tone[11] and occasionally the type of conduction pattern seen may be markedly altered by the administration of propranolol The results also suggest that no test of cardiac conduction performed in the catheterization laboratory can be considered to be specific in the exclusion of the possibility of A V nodal re entry in a patient suspected of having episodes of PSVT In this and other reports[4] not all patients with PSVT developed echo beats during premature atrial stimulation

The results of this study suggest that dual A V nodal pathways are common only in patients with PSVT Although patients without this history may certainly demonstrate this conduction pattern only 7 5 per cent of patients with normal PR intervals without PSVT were found to have dual pathways Dual A V nodal pathways cannot readily be demonstrated in patients with short PR intervals and normal QRS complexes and do not appear to be common in patients with decreased A V nodal function

Summary

Atrioventricular conduction patterns suggestive of dual A V nodal pathways have been reported in patients with and without a history of paroxysmal A V nodal re entrant tachycardia (PSVT) The purpose of this study was to determine whether a significant association exists between this conduction pattern and the occurrence of PSVT in man

The pattern of A V conduction was evaluated at similar pacing rates in 13 patients with documented PSVT and 135 patients without PSVT Patients without PSVT were divided into groups with normal PR intervals (106 patients) PR intervals of 120 msec or less (12 patients) and PR intervals of 200 msec or greater (17 patients)

Evidence of dual A V nodal pathways was found in seven of 13 patients with PSVT and nine of 135 patients without PSVT, including eight of

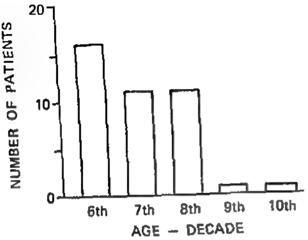

Fig 1 Age histogram of 40 patients with MVP

evidence of rheumatic heart disease Patients with a history of angina pectoris or previous myocardial infarction were also excluded

Results

Clinical features The average age of the group of 40 patients was 65 5 years (range 50 to 90 years) (Fig 1) Fifteen patients were asymptomatic 14 were in Functional Class II 10 were in Class III and one was in Class IV (Table I) Fifteen patients complained of troublesome palpitations Six patients reported atypical chest pain Three patients developed bacterial endocarditis on prolapsing mitral valve leaflets A mid or late systolic click was detected by physical examination and phonocardiography in only 27 patients Nineteen patients had late systolic murmurs in the mitral area the murmur was holosystolic in 10 patients

Roentgenographic findings Cardiomegaly as defined by a cardiothoracic ratio of greater than 50 per cent was noted in 21 patients (Table I) Cardiac series with barium in the esophagus showed left atrial enlargement in 19 and left ventricular enlargement in 21 patients Eighteen patients had both left atrial and left ventricular enlargement six of these patients also had right ventricular enlargement

ECG findings ECG evidence of left ventricular hypertrophy was present in 15 patients and while 14 had p waves suggestive of left atrial enlargement (Table I) Significant arrhythmias consisting of frequent premature atrial or ventricular beats paroxysmal atrial tachycardia atrial flutter or atrial fibrillation occurred in 19 patients

Table I Findings in 40 patients

	No of patients
Symptomatology	
Function Class I	15
Function Class II	14
Function Class III	10
Function Class IV	1
Midsystolic click	27
Murmur	
Late systolic	19
Holosystolic	10
No murmur	11
Thoracic roentgenogram	
Normal	19
Cardiomegaly (C/T 0.50)	21
Left atrial enlargement alone	1
Left ventricular enlargement alone	3
Left atrial and left ventricular enlargement	18
Left atrial and biventricular enlargement	6
ECG	
Normal	15
Left atrial enlargement	14
Left ventricular enlargement	15
Frequent premature beats	7
Atrial fibrillation	14

The most frequent arrhythmia atrial fibrillation was present in 14 of these patients Frequent premature ventricular beats were recorded in only four patients Two patients had complete heart block and three had first degree atrioventricular block. Four patients had Q wave and T wave inversion in Leads II III and aV_F There was no historical evidence of coronary artery disease in these four patients

Phonocardiographic findings A mid or late systolic click was detectable in 36 patients A nonejection type of systolic murmur was recorded in 32 patients it was holosystolic in eight instances There was a variable response in the timing and duration of the click and murmur with the Valsalva maneuver and amyl nitrite inhalation

Echocardiographic findings Each of the 40 patients had unequivocal posterior prolapse of the posterior leaflet of the mitral valve during systole Prolapse of both the posterior and anterior leaflets was detectable in 33 patients (Fig 2) Prolapse was present during more than

The significance of mitral valve prolapse in middle-aged and elderly men

Charles B Higgins M D
Robert T Reinke M D
Barbara B Gosink M D
George R Leopold M D
La Jolla Calif

Substantial evidence has been compiled in recent years to indicate that mid and/or late systolic clicks and murmurs are an indication of the existence of systolic prolapse of the mitral valve apparatus[1-8] The angiographic demonstration of this mitral valve dysfunction was initially reported by Barlow and associates[1] and Segal and Likoff in the early 1960 s In 1970 Shah and Gramiak[9] and Dillon and associates[10] described the echocardiographic finding of posterior prolapse of the leaflets of the mitral valve during the latter part of systole in several patients with angiographically documented mitral valve prolapse Subsequently echocardiography has permitted documentation of this lesion in a large number of patients It is generally held that usually this lesion is an innocuous finding discovered in young and middle aged women[1,3,11] However it has now become apparent that this lesion may be associated with serious hemodynamic impairment[4,7,8,1,14] and troublesome arrhythmias[3,6,8,11,13,15] The purpose of the current study was to determine the significance of this lesion in a consecutive group of middle aged and elderly men with echocardiographic evidence of mitral valve prolapse In order to gain this information the clinical, radiographic echocardiographic phonocardiographic, and electrocardiographic (ECG) data were evaluated in 40 consecutive patients with the unequivocal echocardiographic findings of mitral valve prolapse (MVP)

Methods

The 40 patients included in this study were those male patients older than 50 years of age who were shown by echocardiography to have systolic posterior prolapse of a leaflet of the mitral valve (MVP) between July, 1973 and August 1974 The echocardiograms were performed with the patients in the supine or left decubitus position utilizing a Picker Model EV10 ultrasonoscope and a 2 25 or 3 5 MHZ transducer The transducer crystal measuring ½ inch in diameter was equipped with an acoustic lens which collimated the acoustic beam for 5 cm tissue depth The echocardiograms were recorded either on Polaroid photoprints of the oscilloscopic tracing or upon a strip chart recorder The recordings were obtained with the transducer placed at the left sternal border in the interspaces which provided maximum signals from the free edge of the anterior and posterior leaflets In addition the transducer was manipulated in order to obtain signals from the aortic root and posterior wall of the left atrium

The clinical records thoracic roentgenograms phonocardiograms ECG s and echocardiograms were reviewed in these 40 patients Since most of these patients had not been previously evaluated by the above methods no definite information was available as to the age of onset or duration of MVP Those patients during this period of time who had cineangiocardiographic or echocardiographic evidence of a flail leaflet of the mitral valve were excluded from the study as were those patients with clinical history or laboratory

From the Departments of Radiology University and Veterans Administration Hospitals University of California at San Diego School of Medicine La Jolla Calif

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Reprint requests Charles B Higgins M D Department of Radiology Stanford University Hospital Stanford Calif 94305

early and prolonged pattern of prolapse in seven of 20 patients with echocardiographic and angiographically documented prolapse of the mitral valve Holosystolic prolapse may suggest the presence of a flail leaflet of the mitral valve[1, 20] However both the patients in the current study and those of Popp and associates[7] lacked the paradoxical anterior diastolic movement of the posterior leaflet and apparently did not have a flail leaflet

The initial angiographic observations in mitral valve prolapse syndrome described prolapse limited to part or all of the posterior leaflet in the majority of patients[1,4] It is apparent from the current study that nearly all patients have evidence of prolapse of both mitral valve leaflets Although echocardiographic studies have elicited prolapse of the anterior as well as the posterior leaflet [7] prolapse of the anterior leaflet has been infrequently observed during cinecardioangiography[1,4] It is likely that the use of the right anterior oblique position in which posterior prolapse is easily visualized precludes adequate evaluation of the anterior leaflet Although severe prolapse has been visualized in this position small degrees of prolapse might not be detected since the posterior leaflet may be projected over the anterior leaflet of the valve[7, 8]

Another echocardiographic feature of MVP in these patients was the high closing velocity (EF slope) and excursion of the anterior leaflet All but three of the patients in this subgroup had late systolic or holosystolic murmurs and most had echocardiographic and/or radiographic evidence of left atrial enlargement An increased EF slope appears to be a nonspecific finding in mitral insufficiency since Segal and associates[2] have reported an increased closing velocity and excursion in patients with isolated mitral insufficiency of various etiologies Recently the increased velocity and excursion of the anterior leaflet has been used to indicate a nonrheumatic etiology of mitral insufficiency

While the prevailing view is that the majority of patients with mitral valve *prolapse* are female patients with little cardiac symptomatology [3, 11] several recent reports indicate substantial symptomatology and hemodynamic derangements in selected subgroups of these patients[7, 1, 14] The current study indicates significant cardiac symptomatology in the majority of middle aged and elderly male patients with echocardiographically detectable MVP It must be pointed out however that these patients were referred for echocardiographic evaluation and therefore were selected on this basis It is possible that many patients with MVP go undetected since they may have negligible symptomatology or escape auscultatory detection

In the current study as well as in previous reports[1, 11, 12, 13] there was a high incidence of various arrhythmias Indeed there appears to be a definite danger of sudden premature death in this syndrome presumably due to lethal arrhythmias.[17, 18] The high incidence of atrial fibrillation in the current study is likely on the basis of atrial hypertension and/or enlargement and attests to that hemodynamic significance of the mitral valve dysfunction

Another clinical feature of this syndrome is atypical chest pain [4, 12] While atypical chest pain has been nearly universally present in some selected series of patients with this syndrome it was *an infrequent* occurrence in our patients Indeed it has been suggested that atypical chest pain may be a specific feature in those patients with mitral valve prolapse and cineangiographic *evidence of left* ventricular dyskinesis Hemodynamic and cineangiographic findings have been consistent with a myocardiopathy in these patients Many of these patients have had ECG alterations suggestive of inferior ischemia and/or infarction This pattern was observed in 10 per cent of our patients all of whom had atypical chest pain Thus it appears that the triad of atypical chest pain ECG features of inferior myocardial ischemia and left ventricular asynergy occurs in some patients with mitral valve prolapse However this subgroup appears to comprise only a small minority of patients with mitral valve prolapse

Roentgenographic and/or ECG *evidence of* cardiac enlargement or hypertrophy was evident in 53 per cent of the patients in the current study This was due in most instances to left atrial and/or left ventricular *enlargement* This high incidence of cardiac enlargement is indicative of the hemodynamic significance of this lesion While many earlier reports [3, 7, 11] have indicated that the heart size is usually *normal* in this disease more recent studies indicate that more than one third of patients with mitral valve prolapse display radiographic evidence of *cardiomegaly* or left atrial enlargement[8]

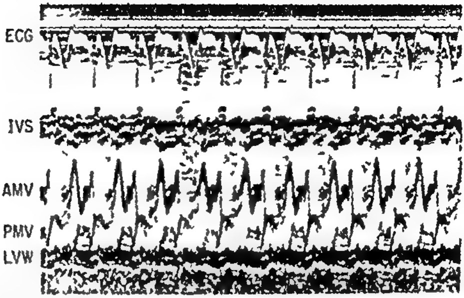

Fig 2 ECG and mitral valve echogram from a patient with a midsystolic click and late systolic murmur demonstrates posterior prolapse of both the anterior (AMV) and posterior leaflets (PMV) of the mitral valve Prolapse was present during more than half of systole Note the separation of the leaflets during the latter portion of systole and the elevated velocity of mitral valve closure Time increments of 0 5 second are indicated by the horizontal distance between dots while spatial increments of 1 cm are indicated by the vertical distance between dots This format is also used in Fig 3 IVS ventricular septum LVW left ventricular wall

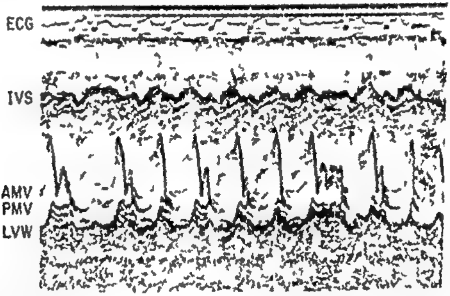

Fig 3 ECG and mitral valve echogram in a patient with cineangiographic evidence of mitral valvular prolapse and insufficiency In this instance there is holosystolic prolapse of both leaflets of the mitral valve

half of systole in 31 patients and holosystolic prolapse occurred in six patients (Fig 3) The EF slope was excessive (> 150 mm per second) in 18 patients and the mitral valve excursion during diastole was increased (> 30 mm) in 12 patients (Figs 2 and 3) Twelve of the patients with an excessive EF slope had echocardiographic evidence of left atrial enlargement

Discussion

Since the initial description of the echocardiographic finding in systolic prolapse of the mitral valve leaflet by Shah and Gramiak[9] and Dillon and associates,[10] prolapse of the mitral valve has been a frequent echocardiographic diagnosis Although initial observations[9, 10, 14] called attention to the localized mid or late systolic timing of the prolapse the current study and others[17, 18] indicate the variable temporal occurrence and duration of the prolapse In the current study the leaflets of the mitral valve prolapsed during more than half of systole in most patients Holosystolic prolapse was present in 15 per cent of the entire group Similarly, Popp and associates[17] noted an

Adrenergic beta blockade and ECG changes in the systolic click murmur syndrome

Edward G Abinader MB BCh MRCPI
Haifa Israel

The multifaceted systolic click murmur syndrome (SCMS) has generated a great deal of interest and has been the subject of many recent publications

Several hypotheses have been advanced but there is as yet no good explanation for the electrocardiographic (ECG) changes associated with this syndrome[1] In an attempt to elucidate these ECG findings we have utilized the propranolol test[2] in 35 patients suffering from the SCMS

Materials and methods

Thirty five patients 18 male and 17 female were studied The mean age was 40 with a range of 12 to 74 years A nonejection click confirmed phonocardiographically was present in all cases None of our patients had any evidence of heart failure or bronchial asthma Familial occurrence was noted in nine cases mother aged 39 and two children aged 13 and 15 years father aged 52 and daughter aged 22 years four siblings belonging to a family of Marfan s syndrome—three brothers aged 33 16 and 12 years respectively and one sister aged 24 years Their parents were not available for examination Another boy aged 14 years suffered from Marfan s syndrome His family was also not available for examination

All patients had their ECG s taken in the fasting state having stopped all medications 72 hours previously After registering a conventional 12 lead ECG in the supine and erect positions adult patients received 40 mg and children 20 mg of propranolol orally One hour later the ECG was retaken in the same positions A Hewlett Packard 1500B ECG was used at a paper speed of 25 mm per second and standardized to give a deflection of 10 mm for 1 mV All traces were analyzed for rate rhythm and morphology with particular reference to the ST segment and T waves in all leads before and after propranolol in the erect and supine positions

Patients were divided into four groups on the basis of the ECG changes following propranolol administration A normalized or markedly improved group B improved group C no change group D deteriorated group

Results

Six patients—three male and three female—belonged to Group A Their ECG s were normalized (Figs 1A to 1D) or markedly improved (Figs 2A and 2B) after propranolol This group included a boy aged 14 with Marfan s syndrome and a boy aged 15 whose mother and sister belonged to Group C

Twenty two of our patients fell into Group B and an example of such a patient s response to propranolol is shown in Fig 3 There were 11 male and 11 female patients with two families falling into this category Four siblings suffered from Marfan s syndrome as well and mitral valve prolapse was confirmed angiographically In six patients belonging to Group C no appreciable or significant change was noted after propranolol

Only one patient belonged to Group D After propranolol the T wave in Lead III increased its negativity from −1 5 mm before to −3 mm after propranolol The ST segment in aV_F became slightly more depressed but the precordial leads showed no deterioration Fig 4 demonstrates the distribution of our patients into the different groups

From the Aba Khoushy School of Medicine Technion Israel Institute of Technology Cardiologic Service Rothschild University Hospital Haifa Israel

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Reprint requests Edward G Abinader MB BCh Rothschild University Hospital The Aba Khoushy School of Medicine P O B 4940 Haifa Israel

Since the clinical profile in the patients in the current study differs from that observed in young patients with MVP, it is possible that symptoms and laboratory signs observed in these older patients represent the long term consequence of this lesion This contention is supported by the high incidence of atrial fibrillation and combined left atrial and left ventricular enlargement Moreover the relatively high frequency of mitral regurgitation in this series suggests the natural history of MVP may be progression to overt valvular insufficiency It must be emphasized however that in most patients in the current study there is no definite evidence that mitral valve prolapse was present early in life An alternate interpretation of the current study is that MVP in older male patients is a result of subclinical myocardial ischemia resulting in depression of myocardial function and more proximate onset of dysfunction of the posterior papillary muscle

In summary the current study indicates that patients with echocardiographically detectable systolic prolapse of the mitral valve display a wide spectrum of clinical and laboratory features While mitral valve prolapse may be an entirely innocent lesion, it is frequently associated with clinical radiographic, and ECG evidence of significant cardiac disease

Summary

The clinical, roentgenographic phonocardiographic ECG and echocardiographic data were evaluated in 40 consecutive middle aged and elderly male patients with echocardiographically detectable systolic prolapse of mitral valve leaflets Prolapse was present during more than half of systole in 31 patients and was holosystolic in six patients In most instances both leaflets prolapsed during systole The closing velocity and excursion of the anterior leaflet were frequently increased particularly in association with evidence of mitral insufficiency A majority of the patients had cardiac symptomatology Moreover, roentgenographic and/or ECG evidence of cardiac enlargment or hypertrophy was evident in 45 per cent of patients with mitral valve prolapse

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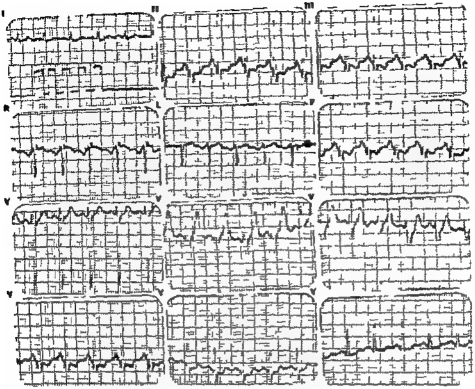

Fig 1C ECG taken in the erect position before propranolol (same patient as in Fig 1A) ST T changes more marked and widespread including V through V with a very ischemic pattern

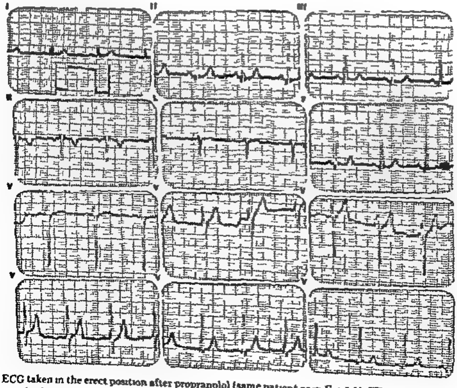

Fig 1D ECG taken in the erect position after propranolol (same patient as in Fig 1A) ST segment now isoelectric and T waves back to normal compared to Fig 1C

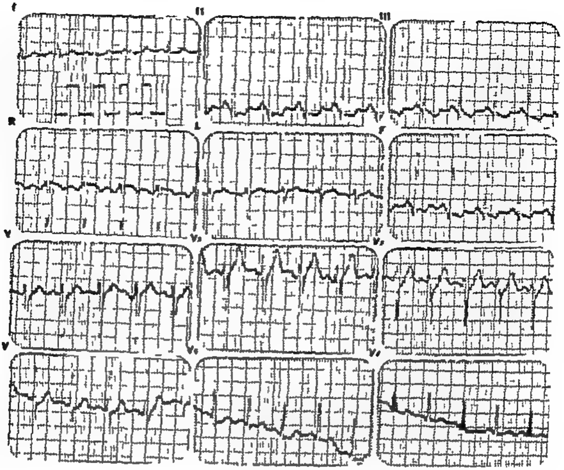

Fig 1A ECG of a patient belonging to Group A taken in the supine position before propranolol showing ST T changes particularly in the inferior leads

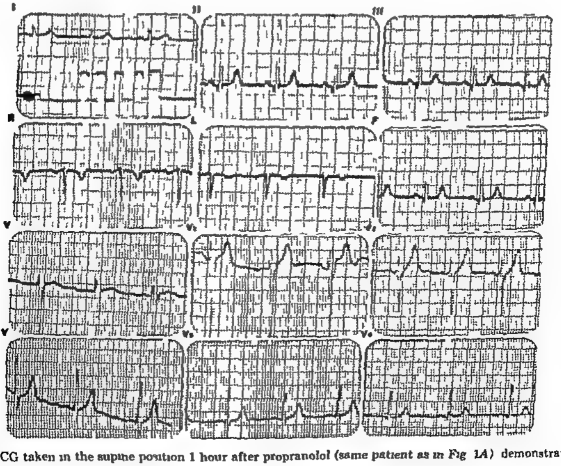

Fig 1B ECG taken in the supine position 1 hour after propranolol (same patient as in *Fig 1A*) demonstrating slowing and normalization of prepropranolol tracing in Fig *1A*

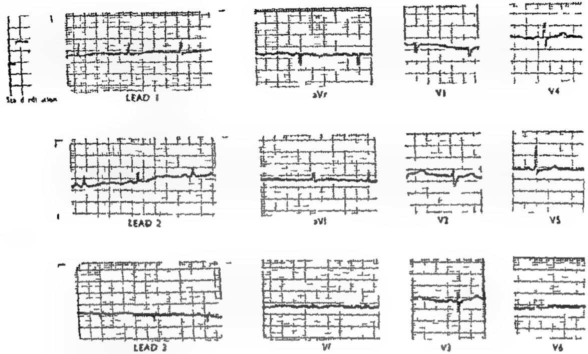

Fig 2B ECG 1 hour after propranolol (same patient as in Fig 2A) demonstrating marked improvement in ST T changes in inferior and precordial leads

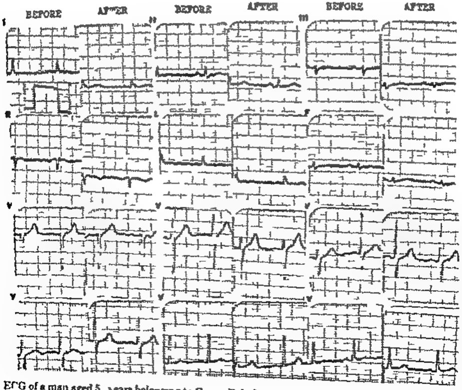

Fig 3 ECG of a man aged 5 years belonging to Group B before and 1 hour after propranolol. Note improvement in T wave amplitude including the left precordial lead

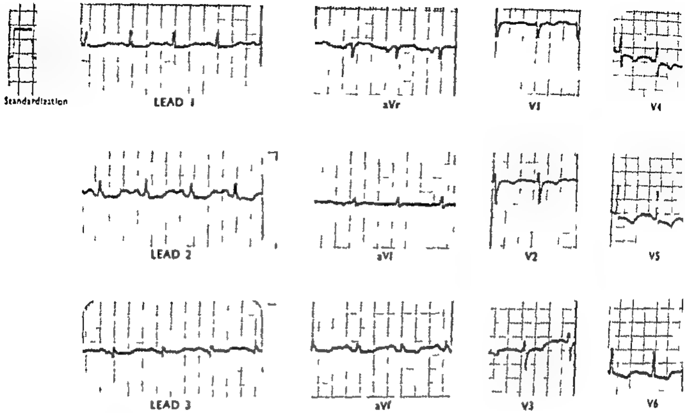

Fig 2A ECG of a patient belonging to Group A taken in the erect position before propranolol

Propranolol had a bradycardiac effect on all patients without troublesome side effects The average pulse in the supine position before propranolol was 75 per minute and after propranolol it was 60 per minute In the erect position the prepropranolol pulse averaged 87 per minute and the postpropranolol pulse was 69 per minute

Discussion

The major ECG abnormalities associated with this syndrome are partially or totally inverted T waves in the inferior leads with or without ST depression, and sometimes involving the left precordial leads and less often the right precordial leads [1] Some authors consider these changes to be due to strain on the papillary muscles and the endocardium secondary to congenital enlargement of the mitral valve leaflet [4] Localized abnormalities in contraction of the heart muscle have been considered by some as the cause of the ECG changes [5] Others have postulated that ischemia of the posterior papillary muscle resulting from excessive stretching may explain these changes [6]

Pockock and Barlow[7] have advanced a similar explanation and considered that the forceful traction on the papillary muscle might occlude or thrombose its rather tennuous vascular supply The compression of the left circumflex artery postulated by some has not been substantiated by coronary angiographic studies [1]

The propranolol test was done on our patients in the fasting state in order to eliminate as much as possible the nonspecific ST T changes found in 2 to 5 per cent of the normal population [9] The majority of our patients 28 out of 35 showed definite ECG improvement 1 hour after propranolol (Fig 4, Groups A and B) These findings speak against an ischemic basis for the explanation of the ECG changes associated with the SCMS and are in accordance with the normal coronary angiographic studies found in the syndrome [1]

Our patients behaved similarly to the noncoronary cases reported by Behar and Kariv,[10] who applied the propranolol test in the assessment of 'nonspecific ST T changes It seems possible that the ECG changes in the SCMS may be due to an autonomic imbalance resulting in sympathetic overactivity The latter possibility is substantiated by the invariable correction or improvement of the ST-T waves following beta blockade Moreover, abnormal sympathetic stim

First degree sinoatrial heart block. Sinoatrial block in the sick-sinus syndrome

Toby R. Engel, M.D.*
Roger C. Bond, M.D.*
Stephen F. Schaal, M.D.
Philadelphia, Pa., and Columbus, Ohio

Sinoatrial (SA) heart block is one of the rhythm disturbances included in the spectrum of the sick sinus syndrome (SSS).[2] The incidence of SA block is uncertain because of inability to recognize latent degrees of block or distinguish high grade block from sinus arrest. Recent observations in the rabbit atrium have demonstrated the existence of perinodal tissues as a possible site of sinoatrial conduction delay. Corollary clinical observations and studies by several groups have suggested that the application of atrial premature depolarizations (APD's) can be used to estimate the conduction interval from sinus node to atrium. The methodology is based on the concepts delineated by Langendorf and associates in determination of sinoatrial conduction delay from the surface electrocardiogram (ECG) in a patient with atrial parasystole.

The purpose of this investigation is to define the abnormalities of sinoatrial conduction in patients with the SSS.

Methods

Thirty-nine patients were studied without premedication in the postabsorptive state. Nineteen were considered to have SSS and 20 were normal control subjects. No cardioactive drugs were received the week prior to study. Informed written consent was obtained from all patients. Atrial electrograms at 40 to 500 Hz and standard ECG Leads I, II, and III at 0.1 to 20 Hz were recorded generally at a paper speed of 100 mm. per second from a bipolar catheter with ring electrodes 1 mm. wide and 1 cm. apart positioned at the high right atrium in the region of the sinus node. Another such catheter was positioned at the lateral wall of the high right atrium for purposes of rapid atrial pacing and application of programmed APD's after every six to eight basic beats during sinus rhythm. Rectangular stimuli 2 msec. in duration at 1½ diastolic threshold were delivered from a Grass Stimulator Model S88 and isolation unit as digitally determined with a Quartec APS 2 programmer. In most instances His bundle electrograms were recorded from a catheter passed via the right femoral vein and positioned across the tricuspid valve.[1]

Sinoatrial recovery times (SART) were measured as the maximal interval to return of spontaneous atrial activity after termination of atrial overdrive suppression.[1] Pacing for 30 to 60 seconds was performed at a variety of heart rates from 80 to 160 per minute. Recovery times corrected for heart rate (CRT) were calculated by subtraction of the basic prepaced cycle length (normal < 390 msec.[11]). Abnormal A-V node conduction was defined as the presence of an atrium-His (A-H) interval 140 msec. or greater[12] or incomplete A-V block with dropped beats, type I (Wenckebach phenomenon) during atrial pacing at 130 b.p.m.[13]

Calculation of SACT. Sinoatrial conduction times (SACT) were estimated from the delay in atrial recovery time after APD's applied in the midportion of atrial diastole where the recovery

From the Departments of Medicine, Medical College of Pennsylvania, Philadelphia, Pa., and Ohio State University College of Medicine, Columbus, Ohio.

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Reprint requests: Toby R. Engel, M.D., 3300 Henry Ave., Philadelphia, Pa. 19129.

*This investigation was performed while Postdoctoral Trainee for the National Heart and Lung Institute.

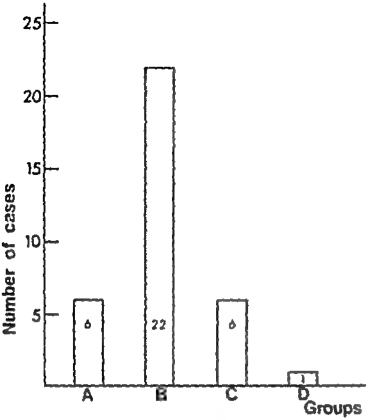

Fig 4 Distribution of our 35 patients according to the ECG changes recorded 1 hour after propranolol See text

ulation may also explain the exaggerated postural sinus tachycardia and increased ventricular irritability often associated with the SCMS Catecholamine studies are now in progress at our laboratory

The striking similarity between the symptomatology and ECG findings in SCMS and cases of neurocirculatory asthenia (NCA) leads us to doubt whether many cases of the so called NCA are not in fact suffering from the SCMS This is made more likely especially in view of the fact that in many cases the click may be missed if the examiner fails to auscultate the patient in different postures All cases labeled as NCA should in our opinion, be reviewed and carefully auscultated in different postures in order to exclude the SCMS

Variability of the T waves with occasional normalization was noted in a few series leading sometimes to the diagnosis of acute coronary episode [1] Coronary artery disease was suspected in 20 of Jeresety's patients who had chest pain associated with ST T changes and in whom coronary arteriograms were done and found normal It is our opinion that the propranolol test may be applied in the SCMS to differentiate ischemic ST T changes from those associated with the syndrome Marked ST T changes such as shown in Figs 1 and 2, could definitely be interpreted as ischemic in nature, however the postpropranolol tracings were against such etiology and further invasive investigations were unwarranted

Summary

In an attempt to elucidate the ECG changes associated with the SCMS we have applied the propranolol test in 35 of our patients suffering from this syndrome To the best of our knowledge this is the first such report in the English literature

Twenty eight patients showed improvement and thus points against an ischemic etiology The test may be applied to differentiate ischemic ST T changes from those associated with the SCMS

We have suggested the possibility of sympathetic overactivity and autonomic imbalance as the basis for the ECG and other features related to the SCMS We have noted the striking similarities in the symptomatology and ECG changes associated with the SCMS and those of neurocirculatory asthenia The implication of this was discussed

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From the Departme ts of Medicine Med cal Coll g of P vl nia Philadelphia Pa, nd Ohio Stat Uni rsity C ll ge of Med in Columbus, Ohi

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Reprint requests Toby R Eng l, M D 3300 H nry A Philad lphia Pa 19129

*This investigation was perf rmed whil Postdoct ral Tra nee for the National H art and Lu g Institute

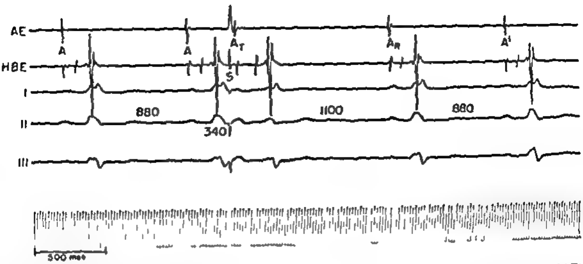

Fig 1 The response to an atrial premature depolarization in a normal patient An atrial electrogram (*AE*) a His bundle electrogram (*HBE*) and three standard leads have been recorded In this instance the basic cycle length (A to A) is 880 msec a test depolarization (A_T) is applied at 340 msec and the recovery interval (A_T to A_R) is 1 100 msec

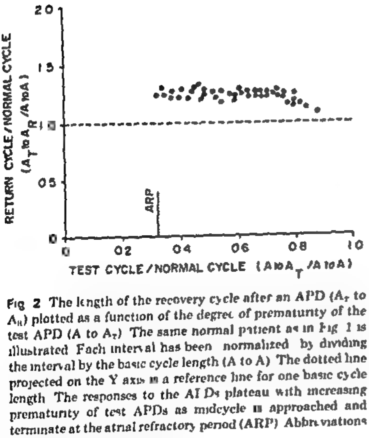

Fig 2 The length of the recovery cycle after an APD (A_T to A_R) plotted as a function of the degree of prematurity of the test APD (A to A_T) The same normal patient as in Fig 1 is illustrated Each interval has been normalized by dividing the interval by the basic cycle length (A to A) The dotted line projected on the Y axis is a reference line for one basic cycle length The responses to the APDs plateau with increasing prematurity of test APDs as midcycle is approached and terminate at the atrial refractory period (ARP) Abbreviations are as in Fig 1

interval was rather constant [5] SACT were estimated only from beats in which the recovery A wave and P wave morphology were very similar to the sinus morphology and in which the sequence of atrial depolarization was unchanged SACT was measured as the recovery time minus the basic cycle length Fig 1 illustrates the response to an APD in a normal patient The atrial potentials are labeled as *A* The atrial potential of the APD is labeled A_T (T for test) The subsequent spontaneous atrial potential is labeled A_R (R for recovery) The next atrial potential is labeled *A'* In the instance illustrated the basic cycle length was 880 msec, with a test APD applied at 340 msec and a recovery interval (A_T A_R) of 1 100 msec SACT is the interval (A_T A_R) minus (A A) and in this instance was 220 msec

Fig 2 illustrates a plot of the atrial recovery time (A_T A_R) as a function of the prematurity of the test stimulus (A A_T) in the same normal patient Each interval has been normalized by dividing the interval by the preceding basic cycle length (A A) With progressive increasing prematurity of test APD s, an interval is reached where further prematurity does not lengthen the recovery interval This has been referred to as a plateau of responses to APD s [5] The calculation of SACT was based on those intervals in the plateau phase of recovery In all but three instances sufficient data were obtained to allow exclusion of values obtained from the first half of atrial diastole in order to minimize possible effects upon automaticity or changes in refractoriness or action potential duration of sinus or perinodal tissues [14, 15] Entrance block, sinus echoes, or abbreviation of sinus cycles seen with very early APD s[15] were excluded from calculations When a plateau of maximal recovery intervals was not achieved before the atrial refractory period, the longest recovery interval obtained from the most premature APD s was used in numerically describing the SACT This underestimated SACT but occurred only in SSS patients, in whom SACT was clearly prolonged

Normal values for SACT were obtained from

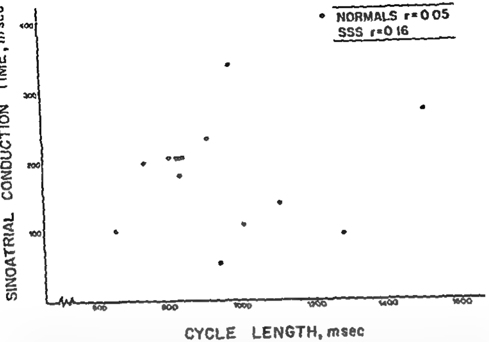

Fig 3 The relationship between cycle length as an index of automaticity and sinoatrial conduction time (SACT) The empty circles represent normal subjects and the filled circles sick sinus syndrome (SSS) patients No correlation is evident between cycle length and SACT in normal subjects (r = [illegible]05) or SSS patients (r = 0 16)

patients with normal heart rates SART s and CRT s and no evidence of A V node or distal conduction abnormalities The distribution of SACT for normal subjects was described as the mean SACT in these patients ± standard deviation (S D) Results were otherwise expressed as mean ± the standard error of the mean (S E M) Statistical comparisons were made with either linear regression analysis or Student s t test with a Hewlett Packard Model 9100 A computer

Results

In 20 normal patients the mean SACT was 169 msec ± 45 5 (S D) with a range of 57 to 231 msec Thus 2 S D above mean SACT for normal subjects was 260 msec

The cycle immediately following recovery (A_R A) was compared to the cycle preceding the APD (A A) in order to estimate the degree to which depression of automaticity with prolongation of sinus cycle length participated in the recovery intervals Prolongation was 3 per cent ± 0 6 (S E M) in the normal patients and was 1 per cent ± 0 9 (S E M) in 19 patients with SSS (see below) Normal patients showed no correlation between basic cycle length and SACT (r =

Table 1 Sinoatrial conduction time in normal patients*

Sex	*Heart rate (b p m)*	*SART (msec)*	*SACT (msec)*	*A A / A A*†
M	72	940	210	1 03
M	63	1070	57	1 01
M	74	1140	179	1 0?
F	70	1160	172	1 03
F	83	1240	114	1 00
[illegible]	78	760	176	1 04
M	85	880	211	1 05
F	80	1000	177	1 06
F	8?	950	2?5	1 05
M	67	< 1250	163	1 00
F	94	< 1250	99	1 01
M	102	690	147	1 03
F	72	1110	172	1 00
M	70	1180	205	1 05
F	71	1100	206	1 0?
M	73	1110	207	1 03
M	65	1060	?31	1 04
[illegible]	83	950	194	1 10
F	[illegible]	800	169	1 01
F	76	1000	1 0	0 99

Patie ts without ymptoms of SS and with ut carotid hypersensi tivity A V o distal conduct n abnormal t es. All ha SART > 1 0 msec a d heart rates above [illegible] b p m

†The rat o f the cycle length following th reco ery interv l to the basic cy le length.

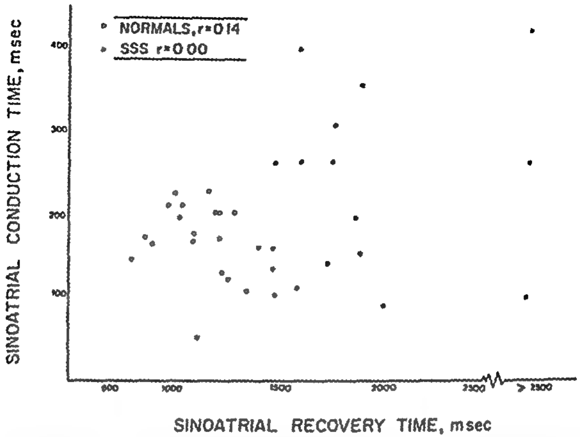

Fig 4 The relationship between sinoatrial recovery time (SART) as an index of automaticity and sinoatrial recovery time (SACT) The empty circles represent normal subjects and the filled circles SSS patients No correlation is evident between SART and SACT in normal subjects (r = 0 14) or SSS patients (r = 0 00)

0 05) or between SART and SACT (r = 0 14) (Table I and Figs 3 and 4) A similar lack of correlation between SACT and cycle length (r = 0 16) or SART (r = 0 00) was found in patients symptomatic with SSS (Table II and Figs 3 and 4)

Nineteen patients with episodic lightheadedness or syncope associated with bradycardia unrelated to medication were considered to have SSS All had SART > 1 250 msec and 15 had CRT > 390 msec Nine of the 19 SSS patients had SACT longer than 2 S D above the mean SACT seen in normal subjects (260 msec) (Table II) Only two of the 19 SSS patients demonstrated intermittent second degree SA block on ECG s or monitored periods prior to study These two patients showed the most prolonged SACT (401 and 426 msec)

The presence of prolonged SA conduction was associated with the presence of abnormal A V nodal conduction (Fig 5) Eight of the 10 SSS patients with abnormal A V nodal conduction as defined in this study had prolonged SACT In contradistinction only two of the nine SSS patients with normal A V conduction had a prolonged SACT

Discussion

Langendorf and associates[9] and later Fleischmann[10] demonstrated that the interval following a premature atrial beat is determined by properties of SA conduction as well as automaticity Numerous investigators[1,8] have found that increasing the prematurity of a single APD does not result in further prolongation of the atrial recovery time in man as might be expected if the dominant effect of the APD were depression of sinus automaticity Instead a plateau of response to progressively more premature APD s is found as is illustrated in Fig 1

The prolongation of recovery time beyond a reset sinus cycle probably for the most part represents SA conduction delay[5,11] SA junctional tissue with distinctive action potential characteristics has been demonstrated in the rabbit right atrial preparation and has been shown to be a potential site of conduction delay[4] Increasing refractoriness of this junctional tissue or the sinus node or portions of the sinus node with increasingly premature stimulation[11] is consistent with the phenomenon of SA entrance block noted in patients[4] Fig 6 offers a diagrammatic explanation for the constant recovery time

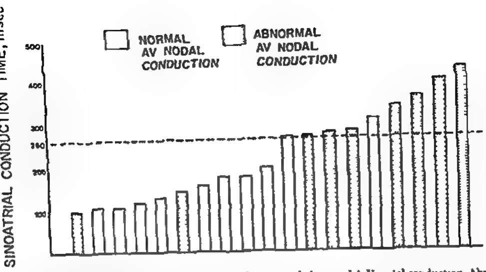

Fig 5 The relationship between prolonged sinoatrial conduction and abnormal A V nodal conduction Abnormal A V nodal conduction was defined as an A H interval 140 msec or greater or intermittent A V block with dropped beats, type I (*Wenckebach phenomenon*) *during atrial pacing* at < 130 b p.m Patients with abnormal A V nodal conduction are illustrated by the stippled bars The horizontal line demarcates 2 S D above mean sinoatrial conduction time in normal subjects

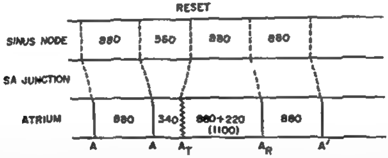

Fig 6 A ladder diagram in explanation of the responses to atrial premature depolarizations in the plateau phase that has been illustrated in Fig. 2 *The premature depolarization recorded in Fig 1* has been used as an example The impulses are generated in the sinus node as illustrated in the upper panel, with a basic cycle length of 880 msec The impulses are conducted through the sinoatrial junction (middle panel) over an interval to the atrium (lower panel) where they may be recorded (A) A test atrial depolarization is applied at 340 msec (A_T) This impulse *ascends the sinoatrial junction over an interval* to discharge the sinus node After a basic cycle length of 880 msec the reset sinus node generates an impulse which descends to be recorded in the atrium (A) The atrial recovery time (A to A) is comprised of (a) the basic cycle length and (b) the interval required for retrograde and antegrade sinoatrial junction conduction

in the plateau phase based on the concept of SA conduction delay There *is an interval* required for a test APD to traverse SA junction tissue in ascent of the impulse to discharge the sinus node After a basic cycle length the *reset sinus* impulse requires another interval in descent to the atrium The atrial recovery time after an APD in mid cycle therefore consists of three components (1) the time of conduction of the test atrial impulse to the sinus node (2) the time of the basic cycle of sinus impulse generation and (3) the time of conduction of the sinus impulse to the atrium where it may be recorded

A reflection of the total time of sinoatrial conduction (SACT) is obtained by subtracting the basic cycle length from the recovery interval in the plateau phase This estimate is the sum of antegrade and retrograde conduction these *may* be of the same order of magnitude as has been shown by simultaneous recordings from rabbit atrium and sinus node during APD s [5] They *may* not always be equivalent and for this reason

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HR (b p m)	SART (msec)	CRT (msec)	SACT (msec)	AH (msec)	Wencke bach	$\frac{A_xA}{AA}$ †
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59	5 000	3 983	104	110	> 160	1 01
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52	1 640	186	14[illegible]	170	90	1 02
49	1 800	576	156	–	160	1 01
60	1 370	370	167	100	> 160	1 01
58	1 300	266	167	90	> 160	0 9[illegible]
49	1 780	5[illegible]6	198	80	160	1 01
57	1 500	447	26[illegible]	120	> 160	99
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properties of A V node conduction when pulse rate changes—as in the case of right atrial pacing with an external pulse generator—then the A H interval varies as a function of pulse rate Analogously the pulse generator presenting stimuli to SA conduction tissue resides in the sinus node A range of normal SACT can be determined only for normal heart rates This range cannot be applied to evaluate SACT in patients with a different set of heart rates as seen with SSS However since slower heart rates should abbreviate SACT patients with bradycardia and prolonged SACT would be expected to have even longer SACT if their heart rates were normal Therefore the range of SACT we report in normal subjects cannot be strictly applied in the exclusion of latent SA conduction abnormalities in patients with bradycardia Comparing SACT in our SSS patients to that of normal subjects tends to underestimate the incidence of abnormal SACT in the SSS group

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Long term survival following aortic valve replacement

Douglas L Roberts M D
James A DeWeese M D
Earle B Mahoney M D
Paul N Yu M D
Rochester N Y

Surgical replacement of diseased aortic valves first introduced in the early sixties [1, 2] has rapidly become the treatment of choice for patients with symptomatic aortic stenosis and/or regurgitation Data have shown that survival of these patients is clearly improved when they have had replacement of this valve [3, 4]

The clinical course and survival rates of the short term survivors of aortic valve replacement have been well delineated [13] It is the purpose of this paper to review the results of prosthetic aortic replacements in our institution with attempts to define the clinical and hemodynamic factors influencing long term survival

Materials and methods

The clinical material includes all patients over the age of 21 undergoing aortic valve replacement at Strong Memorial Hospital between Aug 27 1964 and Dec 31 1970 Patients who had aortic arch repair or replacement of an additional valve at the time of surgery were excluded

A total of 121 patients were so selected, adequate follow up information was available in 119 of these (98 per cent) Age at the time of surgery ranged from 23 to 79 with a mean of 51 years Ninety one were male and 28 were female

Previous aortic valvuloplasty had been performed on two patients Twenty three individuals were judged to have associated mitral valve disease on either clinical surgical hemodynamic or postmortem findings Only four patients were felt to have a hemodynamically significant lesion and underwent mitral commissurotomy at the time of surgery None of the patients required a subsequent operation on the mitral valve

Left and right heart catheterization was performed on 112 of the group The study was done within one month prior to surgery in all but 10 patients in whom the operation was performed 12 to 29 months after cardiac catheterization Of the seven patients who did not undergo cardiac catheterization one had an aortic root angiogram three were considered emergency procedures and in three the operation was performed on the basis of clinical diagnosis only

Classification as to hemodynamic valve lesion was done on the basis of clinical examination cardiac catheterization data and operative findings Those patients with predominant aortic stenosis had a pressure gradient ranging from 45 to 120 mm Hg (mean 79 mm Hg) across the aortic valve There was no significant aortic regurgitation demonstrated by root angiography or surgical observation A diagnosis of predominant aortic regurgitation was made when marked regurgitation was detected at angiography and/or surgery and the aortic pressure gradient was less than 40 mm Hg A lesion was considered combined if there was radiographic evidence of 2+/4 aortic regurgitation and a gradient of over 40 mm Hg across the valve

From the Cardiology Unit Department of Medicine and Department of Surgery University of Rochester School of Medicine and Dentistry and Strong Memorial Hospital, Rochester N Y

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Reprint requests Dr Paul N Yu Cardiology Unit, Strong Memorial Hospital 601 Elmwood Ave Rochester N Y 14642

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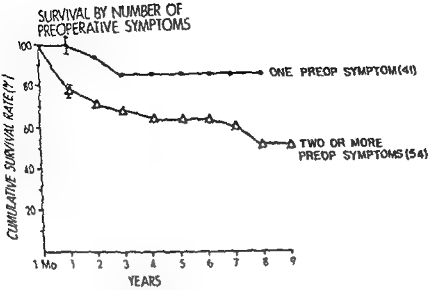

Fig 3 The 41 patients who present with one preoperative symptom (for example angina alone) are compared with 54 patients who had two or more symptoms (i e angina and LVF)

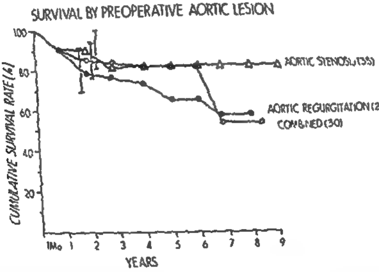

Fig 4 Survival is shown by the type of preoperative lesion

atively The predominant valve lesions in these patients were aortic stenosis (41 per cent) and combined lesions (34 per cent) A marked drop in survival was seen in the patients presenting with angina in the 24 months following surgery

Syncope with or without other symptoms was significantly more common in patients with aortic stenosis (61 per cent) than in those with either combined lesions (28 per cent) or aortic regurgitation (5 per cent) ($p < 0.05$) The survival of the patients with syncope was similar to that of the patients with left ventricular failure

At the end of 7 years a significant difference existed between the survival rate of those with dyspnea and that of the group presenting with angina

Combinations of symptoms were then considered It was found that patients who presented with two or three of the so called cardinal symptoms of aortic disease (left ventricular failure angina and syncope) did worse in terms of both short and long term survival than did the patients presenting with a single complaint (Fig 3) No statistical significance however existed

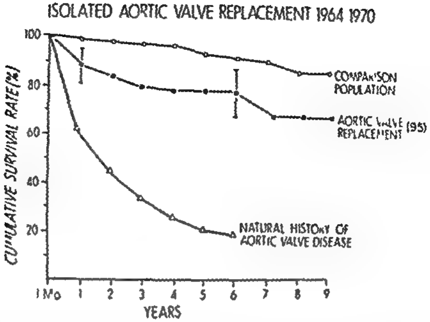

Fig 1 Based on life table analysis over all survival for the entire patient group is shown Each bar denotes one standard error from the mean Expected survival for a normal population matched for age and sex is shown in the upper line and the lower line represents the natural history of untreated aortic valve diseases[1]

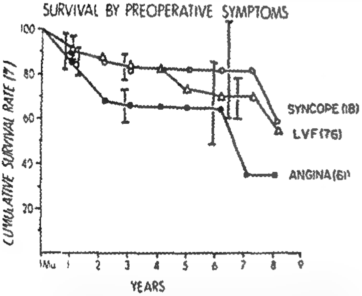

Fig 2 The abbreviation LVF refers to those patients presenting with exertional dyspnea and/or paroxysmal nocturnal dyspnea From the first month to the twenty fourth month a sharp increase in the mortality rate of patients with angina pectoris can be noted The decreased survival in this group of patients continued through the 7 year period

The follow up information was obtained from hospital records Only 15 survivors were not followed on a regular basis at the hospital and information was then supplied by the local physician All data were current as of Jan 1 1973

Results

Overall survival Twenty four (20 per cent) of the total group of 119 patients died within the first month and composed the hospital mortality group These 24 patients were excluded from further analysis Over the years of study there was a decreasing hospital mortality rate to the point where it was only 8 per cent for the 3 years since inclusion in the study ended Also, operative deaths are often considered to be largely due to technical factors and thus conclusions drawn from preoperative data could be erroneous

Fig 1 shows that 18 of the initial 95 survivors of aortic valve replacement died within the first 2 years following surgery (short term survivors) This constituted a 19 per cent mortality rate Seventy seven patients survived beyond 24 months (long term survivors) and only eight deaths occurred in this group during the remainder of the follow up period

Survival judged by presenting complaint In the group of 95 survivors the most frequent preoperative symptoms included exertional dyspnea or paroxysmal nocturnal dyspnea as manifestations of left ventricular failure Seventy six patients with or without other symptoms experienced either or both of these symptoms preoperatively These symptoms were distributed with equal incidence regardless of preoperative valve lesion (stenosis, regurgitation and combined) As shown in Fig 2 the 5 year survival rate for this group was 72 per cent

Of the hospital survivors 61 (64 per cent) experienced symptoms of angina pectoris preoper

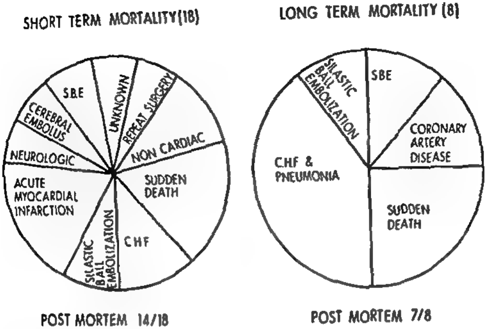

Fig 6 Causes of death in those surviving less than 2 years (short term) and more than 2 years (long term) following surgery are shown Postmortem examinations were performed in the vast majority of the deceased patients.

the stenotic regurgitant and combined groups was nearly identical

Survival judged by valve type Fig 5 displays survival by the various Starr Edwards prostheses used Twenty one survivors received the early model 1000 introduced in 1961 This was replaced by the 1200 series in 1966 and 13 survivors in our series had this valve implanted The model 2300 which used a steel ball as opposed to the silicone rubber ball in the earlier series was first used in 1967 The fact that the valve was functionally stenotic may have accounted for the lowered survival rate in the 15 patients with this prosthesis Patients with the models 1200 and 2310 which was introduced in 1968 showed an improved 5 year survival than those with the earlier prostheses although no statistical significance was present ($p > .05$)

Survival judged by clinical classification The 95 patients were grouped preoperatively according to the clinical classification adopted by the New York State Heart Association Seventy one per cent of the patients were in Class III and 18 per cent were in Class IV Class II patients represented 11 per cent of the series The Class IV individuals showed a higher short term mortality rate (29 vs 14 per cent) than the Class II and Class III patients ($p < 0.05$)

Postoperative symptoms signs and complications Follow up examination on patients surviving the first month after operation was carried out through Dec 31 1972 with a minimum follow up time of 24 months (averaging 50.2) Table I shows the symptoms signs and major complications during the follow up period Note that the symptoms and signs occurred with equal frequency in the short and long term survivors implying no prognostic significance

A diastolic murmur occurred in 37 per cent of these patients at some time during the follow up period and the incidence is higher than that reported in other series[4, 1] This may be due to the length and intensity of the follow up Aortic regurgitation felt to be significant enough to require a second surgical procedure was present in only four patients In a fifth patient an aortocoronary bypass was attempted The mortality rate for reoperation in the five individuals was 60 per cent Three of the four patients with aortic regurgitation had mechanical factors which interfered with valve function—one had thrombosis one had a calcific plaque and one had limited ball mobility[15]

Recurrent exertional dyspnea as a symptom of left ventricular failure was noted in 19 per cent of the survivors during the follow up period but

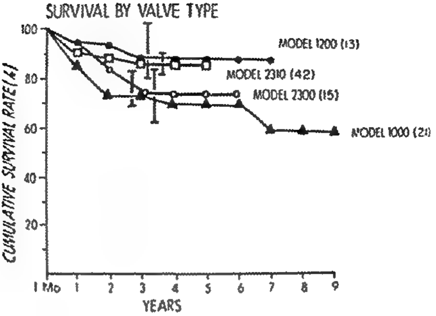

Fig 5 Survival by Starr Edwards prosthetic valves shows increased long term survival from the early 1000 model to the more recent 2310

Table I Symptoms signs and complications of survivors*

Postoperative course	Short term survivors (18) No (1→24 mo)	%	Long term survivors (77) No (>2 yr)	%
Repeat surgery	3	17	2	3
Symptoms				
LVF	3	17	15	19
Angina	4	22	16	21
Syncope	0	0	4	5
Signs				
Diastolic murmur	7	39	28	36
Hemolysis	5	28	20	26
Endocarditis	1	6	4	5
Complications				
Hepatitis	2	11	5	6
Emboli	2	11	7	9
Bleeding	0	0	2	3

*Patients are divided into two survival groups for purposes of comparison The figures in the first column denote the actual number of patients and those in the second column the percentage within the group LVF refers to exertional and paroxysmal nocturnal dyspnea

among the two groups during the follow up period ($0.05 < p < 0.10$)

Patient age or the duration of the preoperative symptoms did not appear to be factors significantly influencing survival

Survival judged by hemodynamic data Resting hemodynamic data were analyzed for determinants of short and long term survival The level of neither the right ventricular systolic pressure nor the left ventricular end diastolic pressure (LVEDP) affected survival The LVEDP was also not a determinant if the group with aortic regurgitation was considered alone

Cardiac index and the level of the left ventricular systolic pressure (LVSP) were not determinants of either short or long term survival The aortic valve area and the systolic pressure gradient across the aortic valve in the group with aortic stenosis did not appear to influence survival

The presence of significant calcium in the valve as determined either radiographically or at surgery was thought to be a possible factor affecting death because of difficulties with the seating of the valve as well as the subsequent aortic regurgitation[11] The 60 patients with calcified valves showed worse long term survival than their 35 noncalcified counterparts but the results were not statistically significant ($p > 0.05$)

Survival judged by preoperative lesion The survivors were divided by the type of preoperative valve lesion 35 patients with aortic stenosis 26 patients with aortic regurgitation and 30 patients with combined stenosis and regurgitation The lesions in four patients could not be classified because of insufficient information

Attempts were then made to compare patient survival among the three groups of patients with these different valve lesions (Fig 4) Survival in

and associates[7] that the type of preoperative aortic valve lesion does not affect survival following valve replacement

The effects of improved prosthetic design can be readily seen in this study Despite a relatively low incidence of postoperative emboli (10 9 per cent) only two episodes occurred in the 2300 series Dislodgement of the silicone rubber ball a cause of death in two patients with the earlier models is a fatal complication which no longer exists

Of the patient group surviving the first month of surgery 63 per cent were alive at the end of the follow up period As noted previously it appeared that once a patient survived the 36 month period his chances for long term survival were excellent The present data coupled with improved methods of handling concomitant coronary artery disease and reduced prosthetic complications increase the attractiveness of aortic valve replacement for those patients with symptomatic aortic valve disease

Summary

Study was made of 95 survivors of aortic valve replacement during the early years of this procedure (1964 to 1970) The average follow up time was 50 2 months

Survival was not related to hemodynamic parameters such as cardiac index or left ventricular pressure and did not appear to be influenced by the type of preoperative valve lesion A history of angina pectoris and a New York Heart Association Class IV grouping were associated with shorter survival

Associated coronary artery disease was a leading cause of death in those patients surviving less than 2 years and angina pectoris the leading cause of morbidity in the long term survivors Sudden death occurred in five patients

Once a patient survived 36 months after the operation the prognosis was excellent

We wish to thank Mrs Margaret Mecredie for her statistical help and Miss Linda Simpson and Mrs Summer King for secretarial assistance

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angina pectoris was the leading cause of disability with an incidence of 21 per cent

Hemolysis occurred in 26 per cent of the patients at some time during the follow up period and in all cases was successfully counteracted by medical therapy

Five patients had endocarditis which carries a high mortality rate in individuals with prosthetic valves[18] Three of them responded satisfactorily to antibiotic treatment and the isolated organisms were, respectively, *Neisseria catarrhalis* enterococcus and microaerophilic streptococcus Organisms were not isolated in the two patients who died of proved endocarditis but in one case candida was isolated from both the valve and the bloodstream at postmortem examination

Hepatitis occurred in seven patients with no long term sequelae Thirteen episodes of cerebral emboli occurred in nine individuals In all but one of these episodes patients had either the model 1000 or 1200 Starr valves 'Silent' emboli particularly renal were not an uncommon finding at postmortem examination however No deaths were noted from anticoagulation but in two of the long term survivors Coumadin therapy was discontinued because of severe bleeding

Causes of death The causes of death in our patient population are shown in Fig 6

In the group of short term survivors, nearly 90 per cent of whom had angina pectoris preoperatively, acute myocardial infarction and sudden death were found with the highest frequency In one of the former patients coronary artery embolism was the cause In two of the three patients with sudden death no etiology could be found at postmortem examination

Three of the eight deaths in the group of long term survivors were caused by left ventricular failure and pneumonia Two more sudden deaths occurred in this group and postmortem examination was carried out in one of these individuals but no cause of death was found In all, 5 per cent of the patients surviving valve replacement died suddenly during the follow up period and this figure compares favorably to that reported in other studies[7, 1]

Discussion

Consideration of aortic valve replacement in a patient with an isolated aortic lesion is influenced by many factors which include natural history of the disease severity of symptoms operative mortality rate, morbidity, and long term survival

One of the major factors which have increased over all survival has been a decreasing operative mortality rate This has been largely for technical reasons and patient selection probably has played a small role

Our data indicate that if patients survive the 30 day period following the operation most deaths occur within the next 36 months Similar findings with a somewhat shorter follow up period have recently been reported by Isom and associates[17]

In evaluating the factors influencing deaths during the first 36 months following operation a preoperative symptom of angina pectoris was found with high frequency (89 per cent) It was therefore not surprising when acute myocardial infarction and sudden death were found to be the leading causes of death in this group, which had a high percentage of postmortem examinations

Ross and Braunwald[18] have in the past demonstrated a high incidence of serious concomitant coronary artery disease in patients with aortic stenosis Linhart and his associates[19] have reported similar findings and found coronary artery disease to be responsible for residual myocardial dysfunction and poor results after aortic valve replacement Our patients were studied before coronary arteriography was routinely performed at our institution but the frequency of angina pectoris in the survival group (21 per cent) postoperatively would also speak for a high incidence of associated coronary disease

On the basis of this we feel that it is currently advisable to perform coronary arteriography on all patients with aortic valve disease and symptoms suggestive of angina pectoris If a critical coronary artery occlusion is found aortocoronary bypass in addition to valve replacement may improve the long term results[20]

Another important determinant of survival following valve replacement is clinical classification of the patient Shean and co workers[7] reported a higher hospital mortality rate for their Class IV patients Similarly Isom and associates[17] showed a decreased long term survival in this group of patients Duvoisin and McGoon[10] found a decreased survival (both short and long term) for their Class III and IV patients following aortic valve replacement and their figures compare favorably to ours

Our findings would agree with those of Isom

and associates that the type of preoperative aortic valve lesion does not affect survival following valve replacement

The effects of improved prosthetic design can be readily seen in this study Despite a relatively low incidence of postoperative emboli (10 9 per cent) only two episodes occurred in the 2300 series Dislodgement of the silicone rubber ball a cause of death in two patients with the earlier models is a fatal complication which no longer exists

Of the patient group surviving the first month of surgery 63 per cent were alive at the end of the follow up period As noted previously it appeared that once a patient survived the 36 month period his chances for long term survival were excellent The present data coupled with improved methods of handling concomitant coronary artery disease and reduced prosthetic complications increase the attractiveness of aortic valve replacement for those patients with symptomatic aortic valve disease

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Diagnosis of Bjork-Shiley aortic valve dysfunction by echocardiography

Premindra A N Chandraratna M D M R C P
Jose M Lopez, M D
Frank J Hildner, M D , F A C C
Philip Samet, M D , F A C C
Jeremiahou Ben Zvi M D
With the technical assistance of
Dale Gindlesperger
Miami Beach and Coral Gables Fla

Patients with prosthetic aortic valves may experience various complications Ball variance resulting in impaction of the ball fragmentation, or embolism has been previously reported[1] Dehiscence of the sewing ring may cause severe aortic insufficiency Thrombosis of the valve may result in systemic embolism or poppet dysfunction with consequent aortic incompetence[2]

Several workers have used noninvasive methods to evaluate prosthetic valve function[3,5] Echocardiography has been demonstrated to be a useful method of detecting prosthetic valve dysfunction[6,7] Douglas and Williams[8] recently outlined the echocardiographic features of the normal Bjork Shiley prosthetic valve This report describes the echocardiographic findings in 22 patients with prosthetic Björk Shiley aortic valves Six of these subjects had prosthetic valve malfunction and a seventh patient had markedly reduced valve clicks due to severe left ventricular dysfunction

Materials and methods

Echocardiography was performed on 26 patients with Bjork Shiley aortic valves Their ages ranged from 26 to 73 years Technically satisfactory records were obtained in 22 patients Fifteen of these patients had no clinical evidence of aortic incompetence or cardiac failure at the time of the ultrasound examination and good prosthetic valve closing clicks were heard in all Of the remaining seven patients two patients had absent valve clicks two had marked reduction in intensity of the closing click and three had significant aortic incompetence with clearly audible valve clicks These seven patients underwent cardiac catherization to assess the degree of valve dysfunction

A commercially available ultrasonoscope, a 2 25 MHz 0 5 inch 7 5 cm focus transducer, and an Electronics for Medicine strip chart recorder were used The patients were examined in the supine position Technically satisfactory records were obtained by using one of three transducer positions (1) third or fourth interspace at the left sternal edge with medial posterior and superior (or slightly inferior) orientation of the transducer (2) second interspace at the left sternal edge with inferior and slight posterior angulation of the transducer, (3) second or third interspace at the right sternal edge with the transducer pointing inferiorly medially and slightly posteriorly In each patient, various transducer angulations were attempted until maximum excursion of the disc was obtained The records were made at a paper speed of 50 mm per second

From the Division of Cardiology Mount Sinai Medical Center Miami Beach and the University of Miami, Coral Gables Fla

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Reprint requests P A N Chandraratna M D Division of Cardiology Mount Sinai Medical Center 4300 Alton Rd Miami Beach Fla 33140

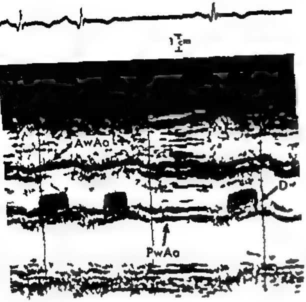

Fig 1 Echocardiogram of a normal Björk Shiley aortic valve recorded from the third left interspace at the left sternal edge Note the rapid opening and closing of the disc (*D*) and the flat systolic segment The anterior (*AwAo*) and posterior wall (*PwAo*) of the aortic root are seen

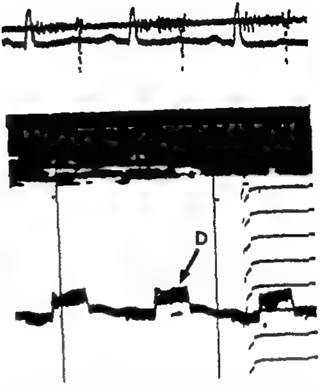

Fig 2 This ultrasound recording of a Björk valve was made by placing the transducer at the right sternal edge and directing the transducer inferiorly posteriorly and medially Movements of the disc (*D*) are seen but the walls of the aortic root are not visualized

Results

Motion of the disc of the Bjork valve was clearly seen in 22 patients The normal echocardiographic pattern of a Bjork Shiley aortic valve (Fig 1) consists of a rapid anterior opening movement of the disc followed by a flat systolic segment Valve closure is indicated by a rapid posterior movement of the disc The anterior displacement of the valve varied from 0 8 to 1 8 cm (mean 1 4 cm.) Fig 1 illustrates the typical pattern of motion seen on the echocardiogram when the transducer is placed in the third or fourth interspace and angulated posteriorly medially and slightly superiorly The anterior and posterior walls of the aorta are clearly visualized and the disc is seen to move within the lumen of the aortic root When the transducer was placed at the right sternal edge and angulated inferiorly posteriorly and medially the walls of the aortic root were not seen and movements of the disc only were noted (Fig 2) The absence of aortic root echoes was probably because the angle of the transducer was such that the aortic root was not perpendicular to the sound beam

Of the seven patients who had cardiac catheterization because of clinical evidence of prosthetic valve dysfunction three were noted to have paraprosthetic leaks with good disc motion Three other patients had extensive clot formation in and around the valve with a fixed immobile partially open disc in two patients and a reduction of disc motion in one patient All three patients had aortic incompetence The seventh patient who presented with marked reduction in the intensity of the closing click had normal disc motion He had marked left ventricular dysfunction and at autopsy a dilated ventricle was found Although some thrombus was found on the rim of the Bjork valve it was felt that the near absence of valve clicks was due to low cardiac output resulting from severe left ventricular dysfunction His echocardiogram showed normal disc movements a dilated right ventricle (3 8 cm) an enlarged left ventricle (6 0 cm) and paradoxical motion of the interventricular septum All three patients with clotted Bjork valves had abnormal

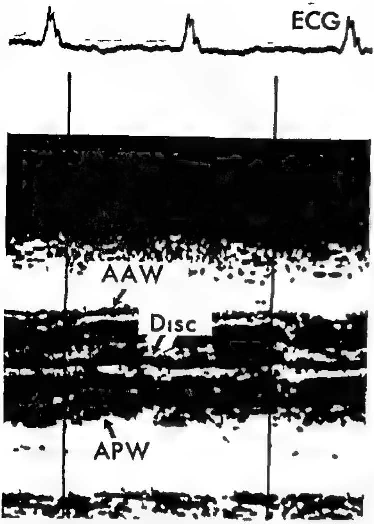

Fig 3 Echocardiogram of the aortic root in a patient with *extensive clot formation in and around the valve* Dense echoes fill the lumen of the aortic root and the posterior wall of the aortic root (*APW*) cannot be clearly identified The linear echo in the center of the lumen may represent the disc of the Bjork valve (From Ben Zvi et al Am J Cardiol 34 538 1974)

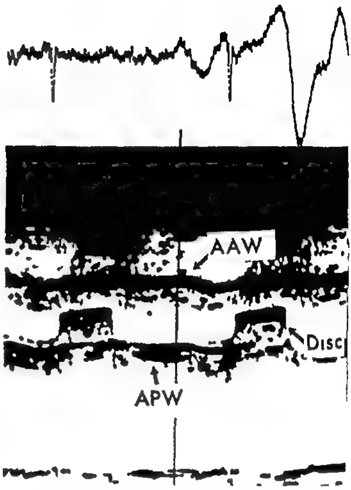

Fig 4 This illustrates the ultrasound tracing of the patient in Fig 3 after surgical removal of the clot Note the excellent motion of the disc of the Bjork valve *AAW* = Anterior wall of the aortic root *APW* = posterior wall of the aortic root (From Ben Zvi et al Am J Cardiol 34 538 1974)

echocardiograms In two patients dense echoes were noted within the aortic root with no discernible disc motion The third patient had a marked reduction of the velocity of opening and closing of the disc

Fig 3 shows the echocardiogram of the aortic root in a patient with a clotted Bjork valve The entire lumen of the aorta is filled with echoes and the posterior wall of the aorta cannot be clearly discerned A linear echo is seen in the middle of the aortic root This may represent the disc of the Bjork valve The echocardiogram (Fig 4), taken after removal of a large clot from the Bjork valve shows excellent disc motion The anterior and posterior walls of the aortic root are now clearly discernible and the dense echoes in the lumen seen on the preoperative echocardiogram are no longer present The initial part of Fig 5 shows the anterior leaflet of the mitral valve of the patient discussed in Fig 3 The transducer was then pointed toward the aortic root Dense echoes seen inside the aortic root represent extensive thrombus formation The pattern is in striking contrast to that of a patient with a normally functioning Bjork valve shown in Fig 6 Movements of the disc are seen and the walls of the aortic root are clearly outlined

Indirect evidence of aortic valve dysfunction was seen on the mitral valve echocardiogram in some patients Fine fluttering of the mitral valve, as depicted in Fig 7 was associated with aortic incompetence and prosthetic valve dysfunction This pattern was seen in four patients (Two of these patients had paraprosthetic leaks and two patients had clotted valves with aortic insuffi

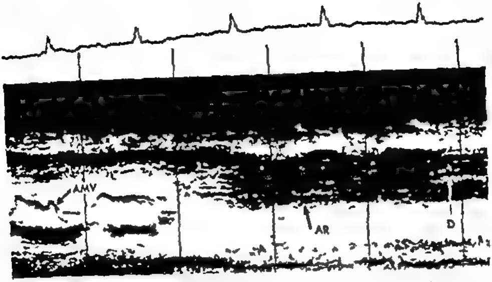

Fig 5 Ultrasound recording showing a M mode scan of the patient in Fig 3 where the transducer was angulated from the mitral valve (to the left of the figure) to the aortic root (right of the figure) The aortic root is filled with dense echoes *AMV* = Anterior leaflet of the mitral valve *AR* = aortic root *D* = disc of the Bjork valve

ciency) Fig 8 illustrates the postoperative (following correction of paraprosthetic leak) echocardiogram of the mitral valve in the same patient as in Fig 7 There is no fluttering seen and the pattern of valve motion is normal The mitral valve echocardiogram of one patient with severe aortic incompetence showed a prolonged AC interval and a shortened PR AC interval of 40 msec (normal > 60 msec) (Fig 9) At catheterization the pulmonary-wedge mean pressure was 18 mm Hg The postoperative echocardiogram showed a normal PR AC interval (70 msec) (Fig 10)

Discussion

Winters and associates have described the echocardiographic features of prosthetic aortic and mitral ball valves They observed that the opening and closing of the poppet was related to the pressure crossover between left atrium and left ventricle for mitral valves and between left ventricle and aorta for aortic valves In a recent report Gibson and his associates have outlined the echocardiographic and phonocardiographic aspects of the Lillehei Kaster mitral disc prosthesis The data from these noninvasive techniques were helpful in confirming the clinical impression of valvular dysfunction in two of their patients

The Bjork Shiley aortic disc prosthesis has been demonstrated to possess certain favorable hemodynamic characteristics such as a low gradient and central laminar flow [9] Reports from other institutions have stressed the paucity of thromboembolic complications in patients who have had aortic valve replacement with Bjork Shiley valves [10, 11] We have recently encountered seven instances of thrombosis on Bjork Shiley aortic valves and the echocardiographic features of one of these patients were illustrated in that report [2] We therefore feel that it is important to perform an echocardiographic examination as soon as possible after Bjork Shiley aortic valve replacement so that each patient could serve as his own control

Using one of three transducer positions described earlier we were able to obtain satisfactory records in 84 per cent of our patients All three patients with valve malfunction caused by extensive clot formation in and around the valve had abnormal echocardiograms A sweep from the mitral valve to the aortic root should be performed in all patients with suspected thrombosis of the prosthesis Dense echoes filling the lumen of the aortic root may be a clue to the presence of extensive clot formation on the valve

The echocardiogram on a patient with almost complete absence of the valve clicks showed good disc motion associated with marked left ventricular dysfunction Thus the absence of marked

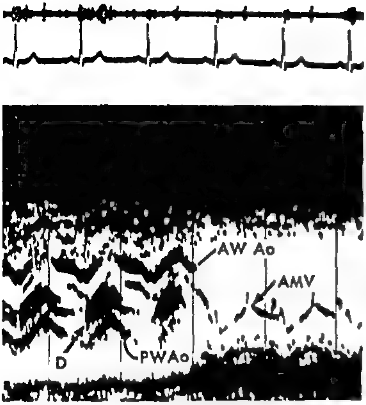

Fig 6 This shows a M mode scan from the aortic root to the mitral valve in a patient with a normally functioning Björk valve The disc (*D*) is seen inside the aortic root *AWAo* = Anterior wall of the aortic root *PWAo* = posterior wall of the aortic root *AMV* = anterior leaflet of the mitral valve

diminution of valve clicks does not always signify thrombosis of the valve

Indirect evidence of prosthetic aortic valve dysfunction may be seen on the mitral valve echocardiogram Fine fluttering of the anterior mitral leaflet denotes aortic incompetence This abnormality disappears when the aortic incompetence is corrected The ultrasound record of the mitral valve in a patient with a massive perivalvular leak showed a prolonged AC interval and shortened PR AC interval indicating a markedly elevated left ventricular end diastolic pressure[8] The PR AC interval returned to normal after correction of the aortic reflux This suggested that the left ventricular end diastolic pressure had decreased

In summary, the echocardiographic features of the normal and malfunctioning Bjork Shiley aortic valves are presented Serial ultrasound studies in patients with prosthetic valves may help in the early detection of valve dysfunction Angiography and surgical intervention in such patients may be effective in avoiding a catastrophic event

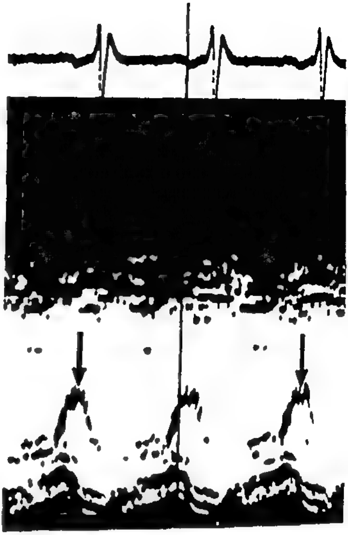

Fig 7 The mitral valve echocardiogram of an incompetent Björk valve is shown The arrows indicate fine fluttering of the anterior leaflet of the mitral valve

Summary

Echocardiography was performed on 26 patients with prosthetic Bjork Shiley aortic valves (BSAV) Technically satisfactory records were obtained in 22 patients The systolic displacement of the valve disc varied from 1 to 1 8 cm (mean 1 4 cm) Six patients developed valve dysfunction Two patients had complete absence of Björk disc motion and dense echoes in the aortic root were noted on the echocardiogram Extensive clot formation in and around the valve was seen at operation After clot removal these two echocardiograms showed excellent disc motion (1 5 and 1 8 cm) In a third patient with a clotted valve marked reduction of the velocity of opening and closing of the valve was noted Three patients had aortic incompetence without evidence of clot formation Normal disc motion (DM) was

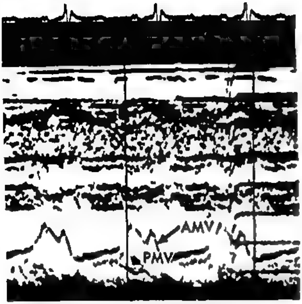

Fig 8 The ultrasound record of the patient referred to in Fig 7 taken after correction of Björk valve dysfunction The anterior (*AMV*) and posterior (*PMV*) leaflets of the mitral valve are seen. There is no fluttering of the anterior mitral leaflet

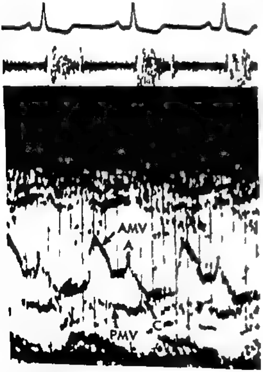

Fig 9 Mitral valve echocardiogram of a patient with severe paraprosthetic aortic regurgitation The prolonged AC interval is evident *AMV* = Anterior mitral leaflet *PMV* = posterior mitral leaflet.

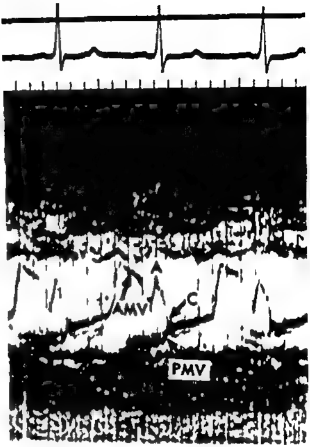

Fig 10 Mitral valve echocardiogram of the patient referred to in Fig 9 taken after correction of the paraprosthetic leak.

observed in all three A seventh patient presented with a low output state and markedly reduced valve clicks Echocardiography revealed normal DM with marked dilatation of the left ventricle These features were confirmed by angiography We conclude that (1) satisfactory echocardiograms can be obtained in most patients with BSAV (2) echocardiography may be a useful method of detecting Bjork valve dysfunction

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Experimental and laboratory reports

Dopamine effects on the intestinal circulation

Wieslaw Pawlik M D
David Mailman Ph D
Linda L Shanbour Ph D
Eugene D Jacobson M D
Houston Texas

Many investigators have been concerned with responses of the normal cardiovascular system to the administration of dopamine (3 4 dihydroxphenylethylamine) Effects of dopamine on the *peripheral* circulation are variable and species dependent In dogs the effect of low doses of dopamine on total peripheral resistance appears to be the result of a balance between vasoconstriction in some peripheral vascular beds and vasodilatation in others including the superior mesenteric and celiac arteries At higher doses dopamine causes constriction of peripheral and visceral vascular beds Effects of dopamine on intestinal blood flow have been studied by several investigators but reports are contradictory Previous studies from our laboratory indicated that dopamine at higher doses consistently decreased mesenteric blood flow in dogs not only under normal conditions but also in various forms of shock.

The finding that dopamine constricted the mesenteric circulation poses the possibility that the drug not only decreases total intestinal blood flow via contraction of mesenteric arteriolar smooth muscle but also that dopamine acts on the precapillary sphincters to reduce perfusion of the vessels from which oxygen is absorbed Thus dopamine could depress intestinal oxygen consumption and induce not only intestinal ischemia but also hypoxia which could lead to necrosis of the gut

The current investigation also had another purpose which was to characterize the pharmacological nature of the receptors mediating the action of dopamine on the smooth muscle of intestinal microcirculatory structures

Methods

Experiments were performed on 27 mongrel dogs of both sexes weighing 15 to 23 kilograms Animals were fasted for 24 hours before the experiment and anesthetized with sodium pentobarbital (30 mg per kilogram) administered intravenously and supplemented as needed Large bore catheters were inserted into both femoral arteries and veins After a midline laparotomy a distal trunk of the superior mesenteric artery supplying a segment of terminal ileum was carefully exposed The ends of the intestinal segment were ligated to prevent perfusion from collateral vessels The mean weight of the segment of intestine was 81 ± 28 (S E) Gm An electromagnetic flow transducer (Micron I D 2 0 mm) was positioned around the mesenteric artery and connected to a blood flow amplifier (Micron) Zero flow was obtained by occluding the artery downstream from the flow probe The first side branch of the superior mesenteric artery distal to the flow probe was isolated and cannulated with a catheter (PE 160) for intra arterial drug infusion After hemostasis an initial dose of 100 U of heparin per kilogram of body weight was given intravenously and supplements of 50 U per kilogram were given at hourly intervals thereafter

A side branch of the mesenteric vein draining the intestinal segment was also cannulated with a

From the Program in Physiology The University of Texas Medical School at Houston and the Biology Department University of Houston Houston Texas

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Reprint requests Eugene D Jacobson M D Program in Physiology The University of Texas Medical School at Houston Texas Medical Center 6400 W Cullen St Houston Texas 770[illegible]

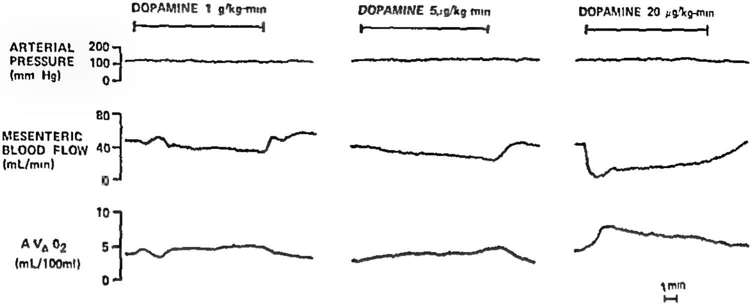

Fig 1 Results of a single experiment in which three doses of dopamine were infused into the mesenteric artery for 10 minutes MBF decreased greatly and *A* $V_A O$ increased slightly hence calculated $\dot{V}o$ decreased Arterial pressure was unaffected

catheter (PE 190) for venous blood sampling and to obtain venous blood for arteriovenous oxygen content determinations A constant flow pump (Cole Parmer Model 7595) withdrew arterial blood from a femoral arterial catheter and venous blood from the mesenteric vein and passed the blood through the arterial and venous cuvettes of a photometric arteriovenous oxygen difference analyzer (Oxford Instrument Company) This instrument provided a continuous direct record of the arteriovenous oxygen difference (A V_A O_2) Venous and arterial effluent from the apparatus was then pumped back to the circulation via a femoral vein At the beginning of each experiment arterial blood was passed through both the arterial and the venous cuvettes to determine zero difference Intestinal oxygen consumption ($\dot{V}o_2$) was calculated from the A V_A O and total intestinal segment blood flow (MBF) and was expressed as milliliters of O per 100 Gm of intestine per minute Systemic arterial pressure was monitored with a pressure transducer (Hewlett Packard 1280C) from a femoral artery MBF A $V_A O_2$, and arterial pressure were monitored in all 27 dogs on a direct writing recorder (Hewlett Packard model 7759A)

In 13 of the animals effective capillary surface area was estimated from the clearance of Rb ^{86}RbCl (Amersham Searle) was diluted in 0 9 per cent saline and was infused intra arterially by a syringe type constant flow pump (Harvard Instruments) at a rate of 10 000 c p m through the mesenteric arterial catheter Six minutes after beginning the infusion three 7 ml samples of mesenteric venous blood were collected in tared gamma counting tubes Preliminary experiments had shown that the Rb concentration in mesenteric vein blood stabilized within 4 minutes Collections were obtained during a control period and after 5 minutes of dopamine infusion before and after haloperidol or propranolol Collection time for the three samples ranged from 1 5 to 6 minutes depending on the flow rate The amount of Rb infused was determined by timed collection of the infusion solution directly from the arterial cannula and then counting the Rb in 7 ml of blood obtained before any isotope had been infused Samples of femoral arterial blood were obtained at the end of each period to determine the concentration of Rb due to isotope which had recirculated through the gut and into the general circulation Samples were usually counted to at least 10 000 counts above background in a gamma counter (Nuclear Chicago) The concentration of Rb in arterial blood was calculated from the amount of Rb infused per minute and the blood flow at that time determined by the flowmeter The product of capillary permeability and surface area (PS product) was calculated from the blood flow and the Rb concentration in the mesenteric vein and artery and was corrected for the small (less than 1 per cent) Rb concentration in the general circulation The equation used was PS = –Q

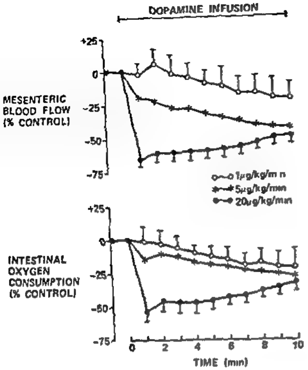

Fig 2 Effects of three doses of dopamine on MBF and $\dot{V}O$ Each value represents the mean ± S E

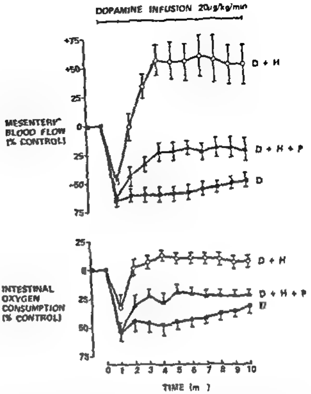

Fig 3 Effects of dopamine (20 μg/kg min) on MBF and $\dot{V}O$ before and after blockade with haloperidol and propranolol *D* = dopamine alone *D* + *H* = dopamine after haloperidol *D* + *H* + *P* = dopamine after combined haloperidol and propranolol

ln(1−E) where PS represents the product of capillary permeability and surface area Q represents blood flow and E the arterial venous extraction ratio During the measuring period all values were relatively constant Since infusion of Rb lasted no longer than 12 minutes no corrections were made for Rb accumulation in the gut tissue nor in the red blood cells

The infusion catheter was connected to the constant infusion pump (Harvard Apparatus) Following a postsurgical interval when MBF arterial pressure and A V_2O had been stable for 20 to 30 minutes intra arterial infusion of dopamine was begun Dopamine (Sigma) was dissolved in 0 9 per cent saline and infusions were carried out for 10 minutes

In separate experiments three doses of dopamine were used 1 0 μg/Kg min (seven dogs) 5 0 μg/Kg min (seven dogs) and 20 μg/Kg min (13 dogs) After cessation of dopamine infusion observations were recorded for 10 minutes in seven of the animals following measurements of arterial pressure MBF and A V_2 O before during and after infusion of the 20 μg/Kg min dose Dopamine receptor blockade was performed with haloperidol (2 0 μg per kilogram McNeil) in saline administered over a 5 minute period directly into the mesenteric arterial catheter Ten minutes after haloperidol was administered dopamine (20 μg/Kg min) was infused again Half an hour after haloperidol administration beta adrenergic receptor blockade was conducted with 0 5 mg of propranolol (Ayerst) infused over a 5 minute period into the mesenteric artery Infusion of the same dose of dopamine was repeated 10 minutes following the propranolol injection

Data were expressed in terms of mean ± standard error and analyzed for statistical significance by the t test for paired values

Results

Mesenteric blood flow (MBF) The initial control value of MBF was 31 5 ± 6 3 ml per minute per 100 Gm of intestinal segment The response to intra arterial infusion of dopamine was a consistent reduction of MBF indicative of local vasoconstriction since arterial blood pressure was unaffected (Figs 1 and 2) The decrease

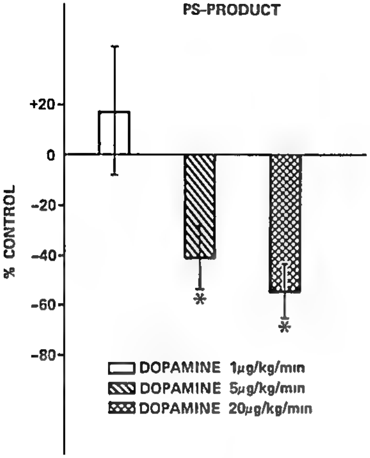

Fig 4 Effects of three doses of dopamine on [86]Rb clearance (PS product) An asterisk indicates a significant change

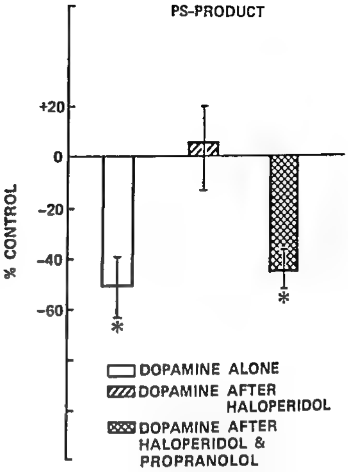

Fig 5 Effects of dopamine on PS product before and after blockade with haloperidol and propranolol An asterisk indicates a significant change

in MBF started within 30 seconds following the onset of drug infusion When dopamine was infused in its lowest and intermediate doses postinfusion hyperemia was observed after cessation of the drug after cessation of the highest dose MBF slowly returned to the control value

At the lowest dose (1 µg/Kg min) dopamine caused an initial fall in MBF in the first minute of infusion followed by a transient small increase in flow over the next minute after which MBF declined steadily throughout the remainder of the 10 minutes infusion period (Fig 2) MBF was significantly ($p < 0.05$) decreased below control values by 7 to 10 minutes after the infusion was begun The mean decrease of MBF at the end of the 10 minute infusion period was 10 per cent ($p < 0.05$)

The intermediate dose of dopamine (5 µg/Kg min) decreased MBF more abruptly than the lesser dose (Fig 2) The decrease at 10 minute of infusion was 33 per cent ($p < 0.001$)

The highest dose of dopamine caused an early decline in MBF, with some autoregulatory escape subsequently (Fig 2) MBF was decreased 56 per cent ($p < 0.001$) by the 20 µg/Kg min dose at the end of the infusion

Following dopamine receptor blockade with haloperidol the 20 µg/Kg min dose of dopamine caused an initial decline in MBF in the first minute of infusion similar to the response before haloperidol (Fig 3) This initial decline in MBF was followed by a rapid increase to a value 50 per cent greater than control ($p < 0.001$) After dopamine receptor blockade beta adrenergic blockade with propranolol was performed which restored subsequent responses to dopamine to a predominantly constrictor effect Thus after combined haloperidol and propranolol treatment dopamine evoked a 25 per cent reduction ($p < 0.001$) in MBF

Intestinal oxygen consumption ($\dot{V}o_2$) Control value for $\dot{V}o$ was 2 7 ± 0 6 ml per minute per 100 Gm $\dot{V}o_2$ was significantly decreased 10 per cent ($p < 0.05$) with the lowest dose of dopamine (Fig 2) Dopamine in its intermediate dose decreased $\dot{V}o_2$ 18 per cent ($p < 0.001$) When the dopamine infusion was stopped $\dot{V}o$ promptly returned to the control level and oscillated for a few minutes above that level The highest dose of dopamine

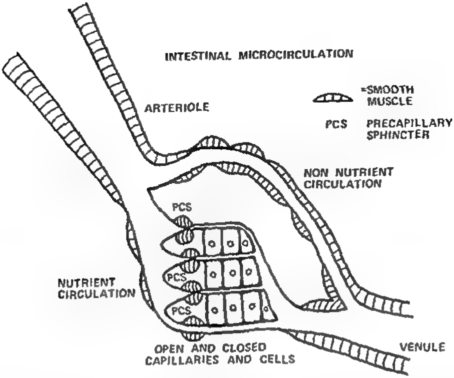

Fig 6 Schematic depiction of the intestinal microcirculation and the smooth muscle elements responsible for its regulation Contraction of the smooth muscle wall of the arteriole would lead to a diminished MBF and an increase in the resistance to blood flow but would not necessarily cause a decrease in capillary perfusion since blood could shunt from the non nutrient to the nutrient circulation A decrease in capillary perfusion would occur if the smooth muscle of the precapillary sphincters contracted thereby closing open capillaries Dopamine decreased MBF Vo and PS product indicating that the agent constricts both arteriolar and PCS smooth muscle causing both ischemia and hypoxia of the gut

rapidly decreased Vo at the end of 10 minutes infusion Vo was reduced 45 per cent ($p < 0.001$)

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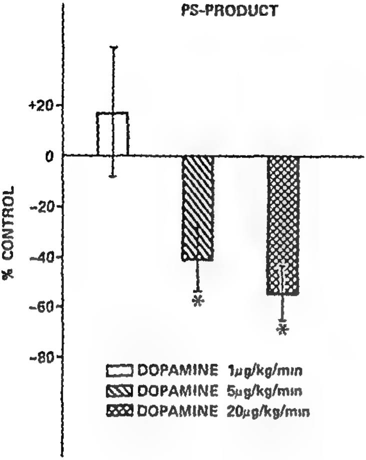
Systemic arterial pressure The mean control value of arterial pressure was 135 ± 15 mm Hg Intra arterial infusions of the three doses of dopamine either before or after the blocking drug did not significantly change the mean systemic arterial pressure (Fig 1)

Discussion

Our results indicate that dopamine is a potent vasoactive drug in the mesenteric circulation producing significant diminution in blood flow through the gut in doses as low as 1 μg/Kg min infused directly into the artery Since systemic arterial pressure was unaffected by intra arterial infusions of the drug dopamine has to be considered a direct vasoconstrictor of the mesenteric circulation Other authors have concluded that dopamine is a vasodilator agent in this circula



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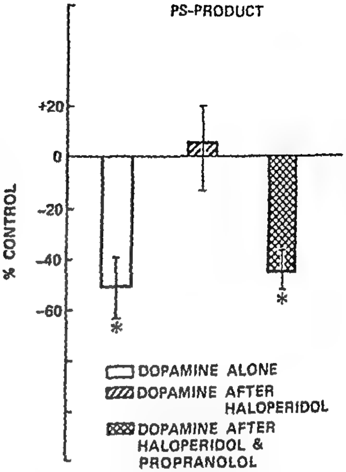

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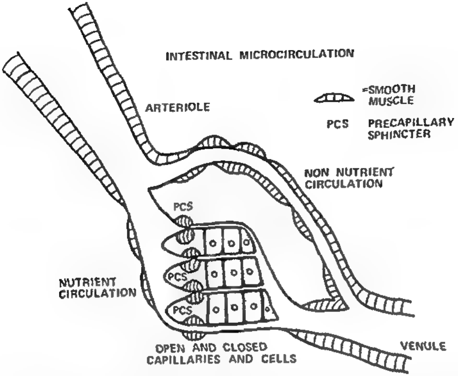

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tion however the doses employed in those reports were small and were injected as a bolus [1, 7] In our experiments the lowest dose (1 $\mu g/Kg$ min) produced a small early increase in blood flow which was transient and gave way to a subsequent decrease in MBF

We also found that dopamine evoked decreases in intestinal uptake of oxygen The declines of V_{O_2} paralleled the decreases in MBF in response to the different doses of dopamine Hence dopamine induced both ischemia and hypoxia in the intestine In this respect dopamine acts upon the mesenteric circulation in a manner similar to most other constrictor agents we have studied except epinephrine which decreases MBF without also diminishing V_{O_2} and PS product [11, 1]

The microcirculatory sites at which constrictor drugs act in the mesenteric vasculatory are the arteriolar smooth muscle which regulates resistance to the total flow of blood through the gut, and the smooth muscle of the precapillary sphincter which regulates the flow of blood through the capillaries These sites are depicted schematically in Fig 6 Since significant oxygen exchanges occur only across the capillary endothelium a reduced uptake of oxygen ensues when blood flow through the capillaries is reduced An accepted measurement of capillary perfusion (the nutrient circulation) is obtained from the clearance of the non metabolized marker Rb (PS product) In our studies dopamine decreased MBF and PS product comparably at the three doses of the drug This suggests that dopamine induces indiscriminate contraction of arteriolar and precapillary sphincteric smooth muscle thereby reducing total blood flow by constricting arterioles and reducing the nutrient circulation by closing capillaries

A specific receptor for the major local circulatory action of dopamine has been predicated [4] This receptor is blocked by haloperidol [1] In the current investigation the mesenteric vasoconstrictor response to dopamine was prevented by haloperidol, as was the diminished uptake of oxygen and the decrease in the nutrient circulation After haloperidol blockade dopamine induced vasodilator responses accompanied by increased V_O These responses in turn, were prevented by beta adrenergic blockade Our findings suggest that dopamine activates at least two receptors in the mesenteric circulation, the predominant receptor which constricts arteriolar and precapillary sphincteric smooth muscle evoking dose related decreases in MBF, V_O and PS product and the occult receptor which relaxes mesenteric vascular smooth muscle thereby increasing MBF and V_{O_2} The second receptor appears to be a peripheral beta adrenergic receptor The dominant receptor may be a unique dopaminergic receptor or it may be the alpha adrenergic receptor In another report the mesenteric vasoconstrictor response to dopamine was prevented by phenoxybenzamine Our findings do not, however answer the questions about the physiological role of dopamine in the mesenteric vasculature

Summary

The effects of intra arterial infusion of dopamine on superior mesenteric artery blood flow, intestinal oxygen consumption and capillary density were studied in anesthetized dogs before and after blockade of dopamine receptors with haloperidol and after beta adrenergic receptor blockade with propranolol Mesenteric blood flow to a distal segment of the small intestine was measured with an electromagnetic blood flow meter and intestinal oxygen consumption was calculated from the measured arteriovenous oxygen difference across the intestine and total blood flow Intestinal capillary density was estimated from the clearance of Rb In normal animals prior to dopaminergic or beta adrenergic blockade dopamine caused a dose related decrease in mesenteric blood flow intestinal oxygen consumption and Rb clearance Only the lowest dose of the drug 1 $\mu g/Kg$ min did not significantly change the intestinal capillary density In dogs pretreated with the dopamine receptor antogonist haloperidol dopamine (20 $\mu g/Kg$ min) caused a significant increase in blood flow and oxygen consumption and did not significantly alter the number of perfused intestinal capillaries These increases in haloperidol blocked animals administered dopamine were reversed by propranolol Our results indicate that dopamine caused smooth muscle contraction in mesenteric arterioles and precapillary sphincters thereby producing intestinal ischemia and hypoxia These findings with haloperidol and propranolol indicate that dopamine stimulates at least two different receptors in the canine mesenteric vascular bed a constrictor receptor blocked by haloperidol and a dilator receptor blocked by propranolol

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The effect of cycle length on cardiac refractory periods in the denervated human heart

D J Goodman, M D
R M Rossen, M D
A K Rider, M D
D C Harrison M D
Stanford Calif

Changes in cycle length have been shown to have important effects on the refractory periods of the atrium and components of the atrioventricular conduction system in animals and man [1-5] Studies in isolated cardiac tissue have demonstrated that variations in cycle length and refractory periods are accompanied by changes in action potential duration [6] Vagal stimulation, acetylcholine and catecholamines can also shorten cardiac refractory periods and action potential duration [3,7]

Of necessity, previous studies in man have been done in innervated hearts, usually in patients with evidence of organic heart disease The transplanted human heart is essentially normal except that cardiac autonomic innervation has been shown to be absent [8,9] This study was carried out to evaluate the effect of cycle length changes on the refractory periods of the atrium, atrioventricular node, and His Purkinje system in the transplanted denervated human heart

Methods

Patient population Eight patients who had successfully undergone cardiac transplantation were studied (Table I) Evaluation was performed at the time of a yearly routine re evaluation All patients were functional New York Heart Association Class I and were receiving immunosuppression with corticosteroids and azathioprine Their weights ranged from 78 6 to 86 4 kilograms and their serum creatinines ranged from 0 8 to 1 2 mg per 100 ml The patients were in sinus rhythm at the time of study and had no electrocardiographic evidence of a conduction abnormality, except for one patient with right bundle branch block (Table I) Informed consent for the studies was obtained from all patients

Electrophysiologic studies His bundle electrograms were recorded with standard techniques [10,11] A tripolar His bundle recording catheter was positioned across the tricuspid valve for recording the His bundle deflection A quadripolar stimulating recording catheter was positioned fluoroscopically against the anterolateral wall of the transplanted right atrium The distal electrode pair was used for atrial pacing and an atrial electrogram was recorded from the proximal pair Interelectrode distances of both tripolar and quadripolar catheters were 1 cm The intracardiac electrograms were transmitted to an Electronics for Medicine DR 16 multichannel oscilloscopic recorder or Hewlett Packard 8811A amplifier with a Honeywell 1508B oscilloscopic recorder, filtered at 40 to 500 Hz and displayed with two simultaneous surface electrocardiographic traces Recordings were made at paper speeds of 100 and 200 mm per second Stimuli were delivered from a Tektronix pulse generator at approximately twice diastolic threshold and of 2 msec duration These were temporally varied by a programmable digital stimulator (M Bloom Philadelphia)

After recording resting intervals refractory

From the Cardiology Division Stanford University School of Medicine Stanford Calif

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Table I Summary of clinical ECG and conduction data*

Patient No	Age	Sex	Years after transplant	Donor rate (b p m)	QRS duration (msec)	P A (msec)	A H (msec)	H V (msec)
1	53	M	1	95	0 12(R)	30	65	40
2	34	M	2	111	0 09	45	90	50
3	34	M	2	83	0 08	35	60	40
4	27	M	1	115	0 10	35	70	35
5	40	M	2	103	0 09	40	60	50
6	44	M	4	107	0 09	25	80	50
7	49	M	1	126	0 10	25	90	55
8	53	M	1	90	0 08	30	75	50

Abbreviations A H = interval between the atrial and the His electrogram recorded from the His catheter H V = interval between the His electrogram and the onset of ventricular depolarization P A = interval between the onset of the P wave and the atrial electrogram recorded from the His catheter R = right bundle branch block.

periods were determined with the extra stimulus technique After every eighth spontaneous or paced beat (S_1) a premature stimulus (S_2) was introduced S_1 S_2 intervals were decreased in 10 msec steps until the effective refractory period of the atrium was reached Refractory periods were measured for at least two different cycle lengths in all patients The range of cycle length variation was limited by the rapid resting rate of the transplanted heart usually greater than 100 beats per minute At the end of the study amyl nitrite and atropine 1 mg intravenously were administered to evaluate the status of the autonomic nervous system

A H and H V intervals were measured as previously described [3] The nomenclature used to identify the intracardiac complexes and definitions of refractory periods are as follows A H, and V represent the atrial His bundle and ventricular electrograms of spontaneous sinus or paced atrial beats (S) A_2 H_2 and V_2 represent the atrial His bundle and ventricular electrograms in response to the premature stimulus (S_2) Atrial effective refractory period = longest S S not resulting in atrial capture by S_2 Atrial functional refractory period = shortest A A_2 interval achievable A V nodal functional refractory period = shortest H H interval achievable by atrial stimulation The relative refractory period of the His Purkinje system = longest H_1 H_2 interval resulting in the pattern of complete bundle branch block Determinations could not be carried out in all patients or at all heart rates because refractoriness of proximal portions of the atrioventricular conduction system prevented testing of more distal portions In this case the effective refractory period of the distal segment was designated as being less than the functional refractory period of the more proximal limiting area The true effective refractory periods could only be less than the designated values in these instances

Results

Electrophysiologic data for the eight patients studied are shown in Tables I and II and displayed graphically in Figs 1 through 4 Control conduction intervals were within the normal limits for our laboratory in all patients (Table I)

The atrial effective refractory period was determined at one or more cycle lengths in all eight patients In seven of the eight atrial effective refractory periods decreased as cycle length shortened (Fig 1) In Patient 3 no change in atrial effective refractory period accompanied the decrease in cycle length Atrial functional refractory periods could be similarly determined in all patients and decreased with shortened cycle length in each case (Fig 2) In Patient 7 the initial decrease in atrial functional refractory period was followed by a slight increase at a still shorter cycle length Atrial arrhythmias complicated determination of atrial effective refractory periods and functional refractory periods in four patients (see below)

The A V nodal effective refractory period could be determined at a minimum of two cycle lengths

The effect of cycle length on cardiac refractory periods in the denervated human heart

D J Goodman M D
R M Rossen M D
A K Rider M D
D C Harrison M D
Stanford Calif

Changes in cycle length have been shown to have important effects on the refractory periods of the atrium and components of the atrioventricular conduction system in animals and man [1-4] Studies in isolated cardiac tissue have demonstrated that variations in cycle length and refractory periods are accompanied by changes in action potential duration [7] Vagal stimulation, acetylcholine, and catecholamines can also shorten cardiac refractory periods and action potential duration [3-7]

Of necessity, previous studies in man have been done in innervated hearts usually in patients with evidence of organic heart disease The transplanted human heart is essentially normal except that cardiac autonomic innervation has been shown to be absent [8,9] This study was carried out to evaluate the effect of cycle length changes on the refractory periods of the atrium, atrioventricular node and His Purkinje system in the transplanted denervated human heart

Methods

Patient population Eight patients who had successfully undergone cardiac transplantation were studied (Table I) Evaluation was performed at the time of a yearly routine re evaluation All patients were functional New York Heart Association Class I and were receiving immunosuppression with corticosteroids and azathioprine Their weights ranged from 78 6 to 86 4 kilograms and their serum creatinines ranged from 0 8 to 1 2 mg per 100 ml The patients were in sinus rhythm at the time of study and had no electrocardiographic evidence of a conduction abnormality, except for one patient with right bundle branch block (Table I) Informed consent for the studies was obtained from all patients

Electrophysiologic studies His bundle electrograms were recorded with standard techniques [10,11] A tripolar His bundle recording catheter was positioned across the tricuspid valve for recording the His bundle deflection A quadripolar stimulating recording catheter was positioned fluoroscopically against the anterolateral wall of the transplanted right atrium The distal electrode pair was used for atrial pacing and an atrial electrogram was recorded from the proximal pair Interelectrode distances of both tripolar and quadripolar catheters were 1 cm The intracardiac electrograms were transmitted to an Electronics for Medicine DR 16 multichannel oscilloscopic recorder or Hewlett Packard 8811A amplifier with a Honeywell 1508B oscilloscopic recorder, filtered at 40 to 500 Hz and displayed with two simultaneous surface electrocardiographic traces Recordings were made at paper speeds of 100 and 200 mm per second Stimuli were delivered from a Tektronix pulse generator at approximately twice diastolic threshold and of 2 msec duration These were temporally varied by a programmable digital stimulator (M Bloom, Philadelphia)

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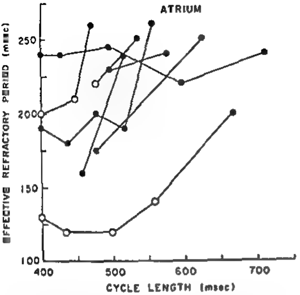

Fig 1 The atrial effective refractory period at different cycle lengths in eight patients. Patients are represented as a series of connected solid circles. Open circles indicate induction of atrial arrhythmias

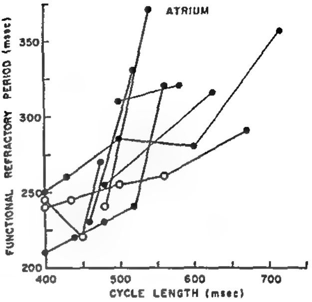

Fig 2 The atrial functional refractory period at different cycle lengths in eight patients. Notation same as Fig 1

At the termination of pacing studies heart rate response to amyl nitrite and atropine 1 mg intravenously was assessed. Atropine produced no change in donor heart rate whereas amyl nitrite produced small (< 5 per cent) changes in heart rate late in the course of its hypotensive effect. These results document autonomic denervation in these patients

Discussion

The effect of cycle length both on action potential duration in isolated cardiac tissues and on refractory periods in animals and human beings has been studied previously. In vitro it can be shown that action potential duration and refractory periods in cells of the atrium ventricle and His-Purkinje system decrease with decreasing cycle length. This observation has been extended to human atrial tissue removed during cardiac surgery. In cells of the A V node recovery of excitability occurs after repolarization is completed.[3] This is most marked at more rapid rates of stimulation. In the denervated canine heart where crushing of the sinoatrial node permits determination of refractory periods over wide ranges of heart rate it has been shown that as cycle length is decreased the refractory periods of the atrium ventricle and A V node shorten. This effect is most pronounced at rapid driving rates e g 200 to 300 msec. Studies in cats with intact cardiac autonomic nervous systems and in innervated patients have documented similar effects of cycle length except that increases in A V nodal effective refractory period accompanied increases in heart rate[5,6]

The transplanted human heart provides a unique situation for extending these observations. At the time of transplantation the donor heart is demonstrated by electrocardiography cardiac catheterization and coronary arteriography to be functionally normal except for its denervated state. At the time our patients were studied they were NYHA Class I with no evidence of electrocardiographic abnormalities except in one patient who manifested right bundle branch block. This is in contrast to most patient studies in which organic heart disease is the rule

The transplanted heart has been shown to be completely denervated[8,9] Administration of amyl nitrite and atropine produced insignificant changes in donor heart rate in our patients. Tyramine has been shown to cause no change in the transplanted heart rate and exercise results in heart rate changes compatible with lack of autonomic reinnervation[8] This permits evaluation of refractory periods free from the influence

Table II Electrophysiologic data*

Patient No	CL (msec)	AERP (msec)	AFRP (msec)	AVNERP (msec)	AVNFRP (msec)	HPSERP (msec)	HPSRRP (msec)	BBRP (msec)
1	630	250	315	< 315	315	315	340	–
	490	175	255	< 255	295	< 295	–	–
2	540	250	370	< 370	390	–	–	–
	490	220†	240†	290	390	–	–	–
3	715	240	355	< 355	< 385	–	–	–
	600	220	280	< 280	360	–	–	–
	500	245	285	290	375	–	–	–
	430	240	260	320	380	–	–	–
	400	240	250	320	370	–	–	–
4	520	240	330	330	400	–	–	–
	460	160	230	250	355	–	–	–
	400	150†	225†	290	375	–	–	–
5	580	240	320	340	375	< 375	–	390(R)
	500	230	310	340	390	< 390	–	–
6	560	260	320	< 320	< 370	–	–	–
	520	190	240	215	325	–	–	–
	480	200	230	< 230	320	–	–	–
	440	180	220	225	315	–	–	–
	400	190	210	230	315	–	–	–
7	475	260	270	< 270	340	< 340	365	395(R)
	450	210†	220†	230	310	< 310	–	–
	400	200†	240†	240	305	–	–	–
8	670	200	290	< 290	350	–	–	–
	560	140†	260†	< 260	370	–	–	–
	500	120†	255†	< 255	375	–	–	–
	435	120†	245†	260	370	–	–	–
	400	130†	240†	250	370	–	–	–

Abbreviations AERP = atrial effective refractory period AFRP = atrial functional refractory period AVNERP = atrioventricular nodal effective refractory period AVNFRP = atrioventricular nodal functional refractory period BBRP = bundle branch refractory period CL = cycle length HPSERP = His Purkinje system effective refractory period HPSRRP = His Purkinje system relative refractory period (R) = right bundle branch block

†Cycle length at which atrial arrhythmias were induced

in six patients but at all cycle lengths in only two patients (Fig 3) Because of the limited number of cycle lengths studied it is difficult to draw firm conclusions although it is apparent that any change in A V nodal effective refractory period with changes in cycle length is small A V nodal functional refractory period was determined in all patients and at all cycle lengths except in two patients Small, inconsistent changes in A V nodal functional refractory periods were found with decreases in four patients increases in three patients and no change in one patient

The relative refractory period of the His Purkinje system could be measured in only two patients and only at the longest cycle length tested Right bundle branch refractory periods were determined in two patients but again only at the longest cycle length The effective refractory period of the His Purkinje system was measured in only one patient and was 315 msec at a cycle length of 630 msec

In four patients atrial arrhythmias which included atrial fibrillation in three and atrial flutter in the fourth were produced These occurred at short paced cycle lengths with close coupling of the premature test stimulus These episodes were of short duration and self limited in three patients, however, in the fourth an episode of atrial flutter lasted 45 minutes requiring rapid atrial pacing for conversion to sinus rhythm

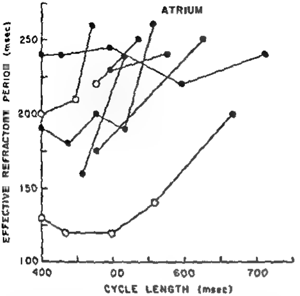

Fig 1 The atrial effective refractory period at different cycle lengths in eight patients Patients are represented as a series of connected solid circles Open circles indicate induction of atrial arrhythmias.

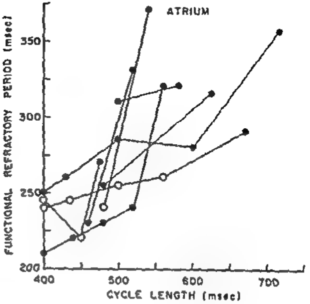

Fig 2 The atrial functional refractory period at different cycle lengths in eight patients Notation same as Fig 1

At the termination of pacing studies heart rate response to amyl nitrite and atropine 1 mg intravenously was assessed Atropine produced no change in donor heart rate whereas amyl nitrite produced small ($<$ 5 per cent) changes in heart rate late in the course of its hypotensive effect These results document autonomic denervation in these patients

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The transplanted human heart provides a unique situation for extending these observations At the time of transplantation the donor heart is demonstrated by electrocardiography cardiac catheterization and coronary arteriography to be functionally normal except for its denervated state At the time our patients were studied, they were NYHA Class I with no evidence of electrocardiographic abnormalities except in one patient who manifested right bundle branch block This is in contrast to most patient studies in which organic heart disease is the rule

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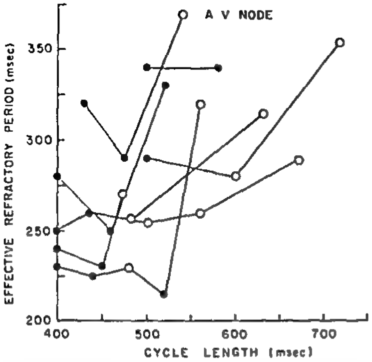

Fig 3 The A V nodal effective refractory period at different cycle lengths in eight patients Patients are represented as a series of connected solid circles Open circles represent the atrial functional refractory period where it exceeded the A V nodal effective refractory period The actual value of the A V nodal effective refractory period is less than the atrial functional refractory period at these points

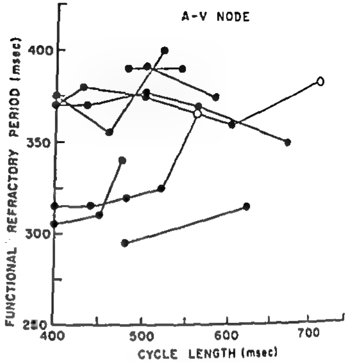

Fig 4 The A V nodal functional refractory period at different cycle lengths in eight patients Notation same as Fig 3

of reflex autonomic adjustments It is well known that the autonomic nervous system may profoundly influence not only heart rate but A V conduction as well[7] That various levels of circulating catecholamines which may affect A V conduction did not influence our results is supported by the finding of a constant heart rate during the entire procedure Our results however were limited by the rapid resting rate found in the transplanted human heart This permitted observations only over small ranges of cycle length a constraint not present in studies on the denervated dog heart, and present to a lesser extent in the intact human heart[1,5]

In spite of this limitation we have shown that the atrial effective refractory period and functional refractory period are responsive to cycle length changes, shortening as cycle length decreases (Table II) This is similar to the finding of Mendez and associates[1] in denervated dogs Cagin and associates[7] in innervated cats, and Denes and associates[6] in the intact human heart The A V nodal effective refractory period could be determined at 16 of 27 cycle lengths studied In these 16 observations, no definite effect of cycle length could be noted It may be that a larger study group would yield significant changes In the intact human heart A V nodal effective refractory period has been shown to increase as cycle length is shortened in contrast to the denervated canine heart, in which A V nodal effective refractory period decreases at rapid driving rates[1,5] These differences have been attributed at least in part to the effect of the autonomic nervous system In our patients, the A V nodal functional refractory period showed no change with cycle length at 25 cycle lengths studied (Table II) Again, it may be that a larger study group would have revealed a small consistent effect Refractory periods of the His Purkinje system could be measured at only one cycle length so that no analysis can be made of the effect of cycle length This is unfortunate, as the greatest decreases in refractory period during shortening of cycle length occurred in the His Purkinje system of the intact human heart[5] This limitation is due to constraints of the functional refractory period of more proximal parts of the A V conduction system (atrium, A V node), which limits delivery of stimuli to more distal parts of the conduction system (A V node His Purkinje system) As demonstrated here and in Denes work, this limits the determination of A V nodal refractory period at slower heart rates and

His Purkinje refractory periods at [redacted] faster heart rate[5]

In four of the eight patients studied atrial arrhythmias were induced at short paced cycle lengths after early test stimuli While it is known that these arrhythmias may be produced by stimulation of the atrium in its relative refractory period their occurrence in otherwise normal hearts has not been common in our experience[16 17] The explanation for their frequent precipitation (4/8 50 per cent) in the denervated human heart is not clear This may very well be related to the lack of autonomic innervation Vagal stimulation or acetylcholine shortens the duration of repolarization of atrial muscle cells[7] This may help to prevent conduction through partially repolarized cells preventing fractionation of wave fronts and the precipitation of atrial fibrillation or re entrant tachycardias The loss of this vagal influence may therefore predispose to atrial arrhythmias In contrast to our results it has been demonstrated that excessive vagal tone may predispose the atria to arrhythmias This discrepancy may be related to variations in autonomic tone producing nonhomogeneity of repolarization and susceptibility to atrial arrhythmias

While the observations made here were performed in the denervated human heart the results have relevance in understanding the electrophysiology of atrioventricular conduction and arrhythmias in patients with heart disease It has been shown that patients with heart disease have defective reflex parasympathetic responses to vasoreceptor stimulation and sympathetic function is known to be abnormal in congestive heart failure [*] Although there [redacted] no evidence that the heart of patients in congestive failure behaves electrophysiologically as does the denervated heart perhaps this blunted autonomic responsiveness explains the high incidence of atrial arrhythmias in these patients

Summary

We have previously demonstrated that the transplanted human heart is functionally denervated With the use of the extra stimulus technique during His bundle electrocardiography refractory periods of the atrioventricular (A V) conduction system were determined at several heart rates after pacing induced changes in cycle length in eight patients who had previously undergone cardiac transplantation

Shortening of the cycle length was accompanied by a decrease in both the effective and functional refractory periods of the atrium No consistent change in A V nodal effective refractory period or functional refractory period could be demonstrated Because A V conduction was limited at shorter cycle lengths by the functional refractory periods of the atrium and A V node bundle branch refractory periods could be determined in three patients only at the longest cycle length studied

In four of the eight patients atrial arrhythmias were produced at short cycle lengths with the introduction of early atrial extra stimuli This may be due to a lack of vagal innervation of the atrium These results contribute to our understanding of atrial arrhythmias

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Sinus slowing produced by intracoronary arterial injections of hyperosmotic solutions in man

Sachiyoshi Abe, M.D.
Masashi Itoh, M.D.
Hiroshi Unakami, M.D.
Takashi Kobayashi, M.D.
Honjo, Japan

Sinus slowing is frequently observed during coronary arteriography.[1-6] Many possible mechanisms have been considered involving a direct action on the sinus node and reflexly mediated parasympathetic stimulation. Indeed, parasympathetic effects seem to be responsible for the sinus slowing because the decreased heart rate produced by coronary arteriography can be prevented by atropine.[7] Carson and Lazzara[8] reported that hyperosmotic solutions, including the contrast material, glucose, and mannitol solutions, produced transient sinus bradycardia when injected into the coronary arteries of the intact anesthetized dogs and the bradycardia was not elicited after bilateral vagotomy. They considered that the bradycardia was reflexly mediated. We observed that hyperosmotic glucose and mannitol solutions can produce transient sinus slowing as well as contrast agent when injected into the human coronary artery. The purpose of this paper is to present our results in the human subjects on comparing the effects of injection of the contrast material, normal saline, hyperosmotic glucose, and mannitol solutions with reference to origin of the sinus node artery.

Material and methods

The tracings of 18 patients undergoing selective coronary arteriography, either for aortocoronary bypass surgery or for establishing the diagnosis of ischemic heart disease, were reviewed. Eighteen patients, comprising 12 men and 6 women and ranging from 33 to 65 year of age, were studied. Arteriograms revealed normal or negligibly narrowed coronary arteries in 14 patients and significant occlusive disease in the remaining four. There was no electrocardiographic evidence of sinus irregularities and rhythm disturbances involving the atria in any of these patients.

The patients were premedicated with meperidine, 35 mg intramuscularly, with an oral administration of 100 mg of pentobarbital sodium. The technique of Judkins[9] or Amplatz and associates was employed for coronary artery catheterization, and that of the left coronary artery was followed by the right in each study. For opacification, 6 mL of 76 per cent Urografin (a mixture of methylglucamine diatrizoate and sodium diatrizoate) was employed. In addition to Urografin, intracoronary arterial injections were made with the same amount of normal saline, 20 per cent glucose and mannitol solutions for the purpose of comparing the effects of injections with these solutions on the sinus rate. Intracoronary injections were performed in this order with (1) saline, (2) glucose solution, (3) mannitol solution, and (4) Urografin. The effects of repeated injections were assured to be negligible with Urografin in five patients. Lead II was continuously recorded in each injection. The change in rate after injection was expressed as a percentage of the control rate. All rates were measured in terms of the P-P interval, and an average of four intervals just before each injection gave the control rate. The maximum sinus slowing was given by

From the Cardiology Division and the Department of Medicine of the Yuri General Hospital, Honjo, Japan.

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Reprint requests: S. Abe, M.D., Cardiology Division, Yuri General Hospital, 38 Higashimachi, Honjo, Akita, Japan.

Table I Changes in the P-P interval produced by intracoronary arterial injection

Case No	Origin of SNA	Left coronary arterial injection											
		Saline			Urografin			Glucose			Mannitol		
		Before	After	ΔP P(%)	Before	After	ΔP P(%)	Before	After	ΔP P(%)	Before	After	ΔP P(%)
1	Left	970	975	1	970	1 170	21	970	1 100	13	960	1 070	11
[illegible]	Right	925	925	0	950	1 130	19	990	1 080	[illegible]	920	1 010	10
3	Left	875	875	0	860	1 050	22	860	960	12	885	990	17
4	Right	540	540	0	540	910	69	570	790	39	540	690	28
5	Left	665	670	1	660	720	[illegible]	660	700	6	670	735	10
6	Left	930	920	−1	930	1 190	28	950	1 120	18	930	1 110	19
7	Right	800	825	3	805	950	18	800	880	10	800	910	14
8	Right	930	930	0	930	1,270	37	910	1 150	26	920	1 100	20
9	Right	670	670	0	700	755	[illegible]	680	740	9	700	785	17
10	Right	680	650	−4	735	[illegible]	31	730	930	27	720	900	25
11	Right	610	610	0	610	790	30	610	710	16	620	730	18
12	Left	690	680	−1	690	775	12	700	790	13	690	780	13
13	Left	680	660	−3	700	890	26	680	735	8	680	740	9
14	Left	935	950	2	935	1 080	16	940	990	5	935	990	[illegible]
15	Right	790	790	0	1 020	1 070	5	810	850	5	790	840	6
16	Right	750	770	3	760	1 190	57	750	890	19	760	930	22
17	Right	960	930	−3	1 010	[illegible]	25	1 000	1 060	6	1 080	1 180	9
18	Right	1 200	1,210	1	1 180	[illegible]	31	1 170	1 230	5	1 190	1 190	0
	Mean	812 2	811 1	−0 06	832 5	1039 2	25 8	821 1	928 1	13 7	821 7	926 1	13.5
	S D	167 0	169 7	1 9	168 8	217 8	16 3	168 1	166 7	9 3	168.1	159 8	7 3

the longest P P interval recorded *after* injection Statistical comparison was made with Student's t test

Results

Among the 18 patients studied blood supply to the sinus node was seen arteriographically to originate from the left circumflex artery by way of the sinus node artery (SNA) in seven patients (39 per cent) and from the right coronary artery in the remaining 11 (61 per cent) In our series no dual blood supply to the node originating from both the left circumflex and the right coronary arteries was observed (Table I)

Isosmotic saline solution produced no significant change in the P P interval when injected either into the left or right coronary artery ($P >$ 0 5) On the other hand intracoronary arterial injections of Urografin and hyperosmotic glucose and mannitol solutions caused significantly increased P P interval when injected into either coronary artery ($P <$ 0 001) Among these solutions, Urografin produced the most marked change in the sinus rate with an intracoronary arterial injection There was significant difference between the change in the P P interval produced by intracoronary injections of Urografin and that of hyperosmotic glucose solutions ($P <$ 0 001) and the effect of intracoronary injection of mannitol solution also differed significantly from that of Urografin ($P <$ 0 01) No significant difference was detected however between the effect of 20 per cent glucose and that of mannitol ($P >$ 0 5) (Table I Figs 1 and 2)

As is shown in Figs 1 and 2 in most patients the sinus slowing began about 2 seconds after the start of intracoronary arterial injections of Urografin was most marked at about 7 seconds, and then returned to control levels by 20 seconds The time course of the changes in the P P interval appeared more rapid with the injection of hyperosmotic glucose and mannitol solutions than following the contrast material

With 76 per cent Urografin sinus slowing resulting from left coronary arterial injections did not differ significantly from the slowing produced by right coronary injections ($P >$ 0 1) Moreover no significant difference in degree of the slowing was detectable between left and right coronary injections with hyperosmotic glucose and mannitol solutions ($P >$ 0 1) (Table I)

Comparison was made between effects of left

Right coronary arterial injection											
Saline			Urografin			Glucose			Mannitol		
Before	After	ΔP P(%)	Before	After	ΔP P(%)	Before	After	ΔP P(%)	Before	After	ΔP P(%)
9 0	970	0	1 020	1 1.0	13	990	1 050	6	990	1 070	8
930	935	1	920	1,300	41	930	1 020	10	930	1 040	12
1,050	1 0.0	0	990	1 050	6	1 000	1 035	4	1 050	1 090	4
660	680	3	640	800	25	640	735	15	660	760	15
770	720	0	720	780	8	680	720	6	00	745	6
1,010	1 000	−1	1 015	1 420	40	1 100	1 440	31	110	145	32
870	870	0	8,0	1 050	21	825	910	10	850	970	8
975	975	0	9,5	1 290	37	960	1,210	26	980	1,235	26
690	710	3	700	790	13	695	790	14	700	790	13
780	50	−4	785	1 070	36	775	810	5	7,0	800	4
600	610	2	610	870	34	620	760	23	610	755	24
730	730	0	730	1 060	45	750	890	19	730	870	19
65	760	−1	755	925	23	760	845	11	770	855	11
960	960	0	990	1 580	60	980	140	44	965	1 350	40
830	830	0	900	950	6	820	910	11	780	830	[illegible]
80	790	1	830	1 500	81	790	1,260	59	800	1,280	60
770	750	−3	750	1 270	69	50	980	31	750	1 100	47
1 000	1 100	10	1 000	2 430	143	1 070	2,210	117	1 040	1 330	[illegible]
838 3	788 3	0 6	844 4	1 179 7	38 7	838 1	984 2	24 6	786 1	942 5	20 2
135 9	213 6	2 9	137 2	397 2	34 7	143 0	409 2	27 4	216 1	287 1	16 1

and right coronary arterial injections with reference to origin of the sinus node artery In seven patients from the group with the sinus node artery originating from the left circumflex artery no significant difference in sinus slowing was noted between left and right coronary arterial injections with Urografin hyperosmotic glucose and mannitol solutions (P > 0 2) Furthermore in 11 patients with the nodal artery from the right main coronary artery injections into the left coronary artery with these solutions resulted in sinus slowing which did not significantly differ in degree from the slowing produced by right coronary injections (P > 0 2) (Table I)

Discussion

Carson and Lazzara first reported that hyperosmotic solutions of substances including polyvinyl pyrrolidone the contrast material sodium chloride glucose sucrose and mannitol produced transient sinus bradycardia when injected into the coronary arteries of dogs and the bradycardia was not elicited after bilateral vagotomy They believed that the bradycardia was reflex mediated from their observations that the same changes occurred with acute coronary venous hypertension induced by coronary sinus obstruction We also confirmed that intracoronary arterial injections of hyperosmotic glucose (1 3 Osm per kilogram of water) and mannitol (1 2 Osm per kilogram of water) and Urografin (1 9 Osm per kilogram of water) produced transient sinus slowing in the human subjects whereas isosmotic saline (0 3 Osm per kilogram of water) had no effect on the sinus rate Sinus slowing produced by intracoronary injections of Urografin with the highest osmolality was most marked among these hyperosmotic solutions

The human sinus node receives its blood supply by way of the sinus node artery James[10] described that the sinus node artery communicated with other atrial arteries of both ipsilateral and contralateral origin but the primary arterial supply of the node was virtually always unilaterally derived More recently Kennel and Titus[1] also demonstrated these anastomoses in the human heart using a postmortem injection technique The functional importance of these anastomotic connections in the dog has been suggested by experimental studies[1 13] but it has not so far been elucidated in the human heart and it is commonly accepted that the sinus node owes

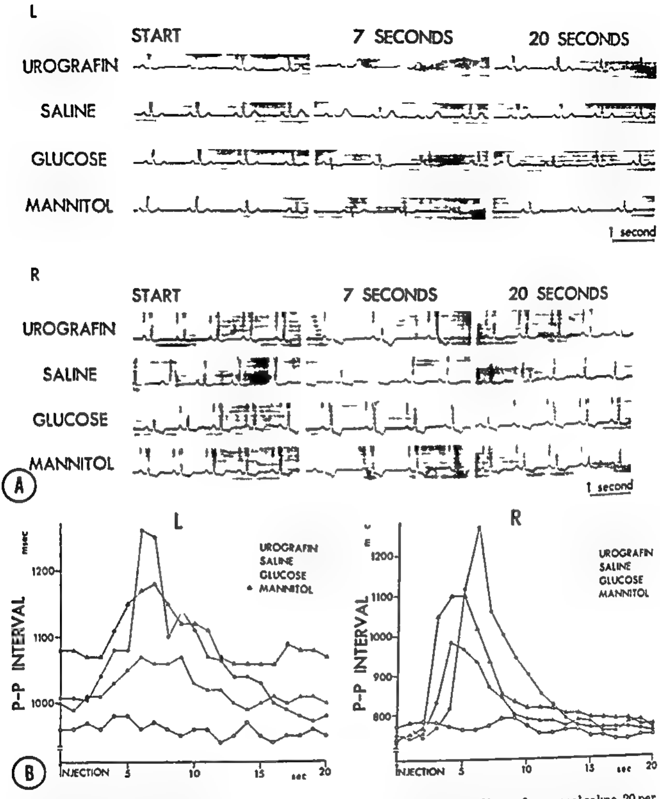

Fig 1 An example of the effect of intracoronary arterial injection with 76 per cent Urografin normal saline 20 per cent glucose and mannitol solutions (case 17) *A* Lead II of the ECG recorded at the start of injection 7 seconds and 20 seconds after the beginning of left (*L*) and right (*R*) coronary arterial injection *B* Time course of the changes in the P P interval partially shown in the above tracings produced by intracoronary injection with Urografin (filled circles) saline (open circles) glucose (filled triangles) and mannitol (open triangles)

its blood supply mainly to the side which gives origin to the sinus node artery From our data there was no significant difference between the degree of sinus slowing produced by an intracoronary injection of hyperosmotic solution into the parent artery of the sinus node artery and the slowing resulting from a contralateral injection If the slowing were a result of perfusion of the sinus nodal area with these hyperosmotic solutions ipsilateral injections might produce more

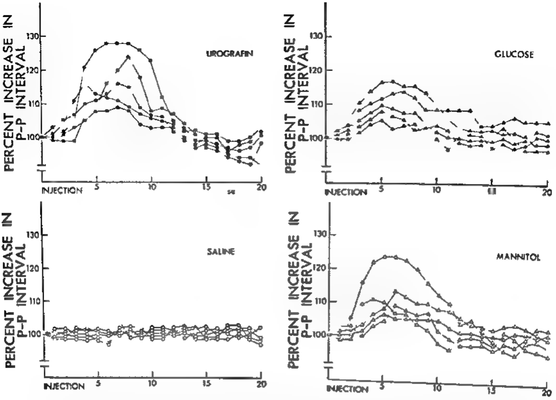

Fig 2A The effect of left intracoronary arterial injection with 76 per cent Urografin normal saline 20 per cent glucose and mannitol solutions in five patients (cases 1 7 11 13 and 15) Note sinus slowing resulted from intracoronary injections of hyperosmotic solutions in contrast with unchanged sinus rate following injection of isosmotic saline

marked change in the sinus rate than contralateral injections Hence it is unlikely that perfusion of the sinus node with these solutions would be responsible for the sinus slowing Therefore both hypoxia and elevated perfusion pressure in the sinus nodal region [5] can be ruled out as causative factors of this slowing For the same reason an action on the efferent endings of the parasympathetic nerve located in the sinus node not through reflex mechanism (e g potentiation of acetylcholine liberated from the nerve terminals) can be excluded as well as a direct effect on pacemaker cells in the area Here reflex mediated parasympathetic stimulation is reasonably considered to be the mechanism of sinus slowing resulting from intracoronary arterial injection of hyperosmotic solutions

Carson and Lazzara postulated that coronary stretch receptors located at the level of capillaries or small veins were fired with dilatation of veins or capillaries induced by transfer of fluid into capillaries due to perfusion of hyperosmotic solutions Our observations also support the concept that hyperosmotic solution when injected into the coronary artery has a negative chronotropic effect on the sinus node through reflex mechanism Indeed the sinus rate is altered by reflexes originating from a number of cardiac receptors[16] located in the atria the ventricles and the coronary artery which are believed to be baroreceptors exclusively No osmoreceptors have been demonstrated in the heart Therefore it is likely that cardiac baroreceptors may respond to an osmotic effect as well. Further investigations may be necessary to elucidate the (intracardiac) location of the cardiac stretch receptors reacting to hyperosmotic solutions and the mechanism of firing the receptors with an injection of these solutions

Summary

The effect of intracoronary arterial injections of normal saline contrast agent hyperosmotic glucose and mannitol solutions on the sinus rate

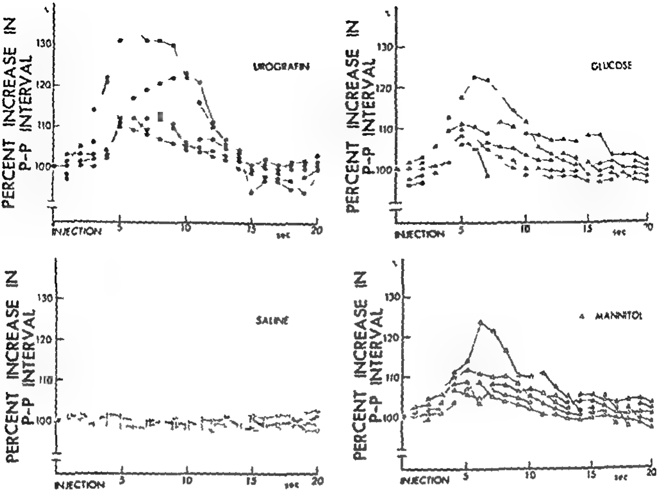

Fig 2B The effect of right intracoronary arterial injection as in Fig 2A

was studied in 18 patients Sinus slowing was not produced by isosmotic saline (0 3 Osm per kilogram of water) when injected into either coronary artery whereas 76 per cent Urografin (1 9 Osm per kilogram of water) 20 per cent glucose (1 3 Osm per kilogram of water) and mannitol (1 2 Osm per kilogram of water) decreased the sinus rate significantly ($P < 0\,001$) Among these solutions Urografin with the highest osmolality produced the most marked sinus slowing whereas no significant difference was detected between change in the sinus rate with hyperosmotic glucose and mannitol solutions ($P > 0\,5$) Moreover, there was no significant difference between the degree of sinus slowing produced by intracoronary injections into the coronary artery of the side which the sinus node artery originated from and the slowing produced by contralateral injections with hyperosmotic solutions ($P > 0\,2$) Therefore it seems unlikely that this sinus slowing would be a result of a direct action on the sinus node including hypoxia and elevated perfusion pressure Reflex mediated parasympathetic stimulation may be operative

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An inexpensive receiver for ECG telemetry

Herman N Uhley M D *
San Francisco Calif

Technical advances in solid state electronics and miniaturization have led to the development of integrated circuits These units characteristically contain many components in extremely small packages Recently a portable ECG telephone transmitter, primarily consisting of two integrated circuits has been described[1] The device which is inexpensive and easy to construct, offers the physician an opportunity to remotely monitor patients with a variety of diagnostic problems, such as arrhythmias or possible electronic pacemaker failure Although the unit functions with various available telemetry receivers, there is a need for a portable, easy to construct inexpensive receiver to provide a complete ECG telemetry system

It is the purpose of this article to describe a simple device utilizing only one inexpensive integrated circuit and a few components, which when used in conjunction with a standard telephone amplifier and an ECG machine functions as a telemetry receiver (Fig 1) Thus, a tone from a remote ECG telephone transmitter can be converted by this device into a graphic record (Fig 2)

Method

An ECG transmitter develops a modulated tone that is sent through the telephone system A standard telephone amplifier coupled electromagnetically to the telephone signal amplifies the ECG tone The amplified signal is taken from the amplifier output transformer or speaker terminals and is fed to the demodulator circuit (Fig 3) The output of the demodulator passes through a low pass filter and presents the original ECG wave form to Lead I of a standard ECG recorder

***Table I** Components of the ECG demodulator circuit*

R_1 10k ohms, ¼ watt
R_2 15k ohms ¼ watt
R_3 100k ohms ¼ watt
R_4 200 ohms ¼ watt
C_1 0 02 μfd
C_2 0 1 μfd
C_3 0 001 μfd
C_4 50 μfd 50 WVDC
C_5 0 1 μfd
IC—NE 565 Signetics or LM 565—Radio Shack
Switch—DPST
Battery—9V
Miscellaneous parts—circuit board wire battery clips, 3 alligator clips IC socket
The telephone amplifier used is an Airphone telephone amplifier 6A [illegible] (Lafayette Radio)

Discussion

One particular integrated circuit called a phase locked loop which costs approximately $3 has the capability of decoding a frequency modulated ECG signal when a few resistors condensers and batteries are added The frequencies of the telephone transmitter and demodulator should be approximately the same, and the receiver frequency can be adjusted according to the formula

$$\text{Frequency} = \frac{1}{4R_1 C_1}$$

R_1 should be within the range of 2 000 to 20,000 ohms with an optional value of approximately

From the Department of Electrocardiography and Coronary Care Unit Mount Zion Hospital and Medical Center San Francisco Calif

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Reprint requests Herman N Uhley M D Mount Zion Hospital and Medical Center P O Box 7921 San Francisco Calif 94120

*Associate Chief of Medicine in charge Department of Electrocardiography and Coronary Care Unit

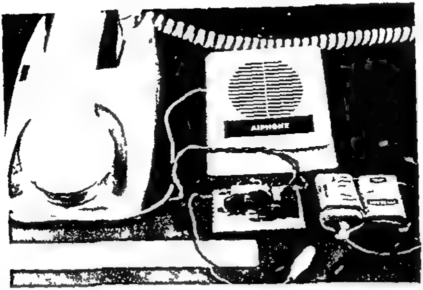

Fig 1 ECG telemetry receiver The telephone rests on a cradle which contains an electromagnetically coupled telephone amplifier The amplifier extension speaker box contains the on-off slide switch demodulator circuit board and batteries (shown in front of the speaker) The clip leads attach to the RA LA and RL leads of the ECG

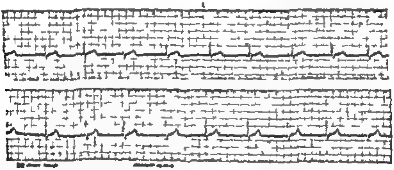

Fig 2 Note the similarity between an electrocardiogram taken with the telephone telemetry system (*top*) and an ECG from the same patient with direct connections to the chest electrodes (*bottom*)

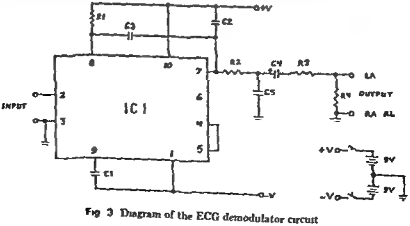

Fig 3 Diagram of the ECG demodulator circuit

4,000 ohms. The value of C_1 should then be determined from the foregoing equation.[2] The output of the demodulator is filtered and fed to Lead I of the electrocardiogram (left arm, positive, right arm and right leg negative and ground). The relatively few components in the circuit presented (Table I) make it easy to construct, and the costs are less than $20 (including the telephone amplifier). Thus it is possible for interested individuals to set up a complete ECG telemetry system at minimal cost utilizing the previously described transmitter[1] with this receiver.

Summary

A simple inexpensive ECG demodulator circuit has been described which may be used in conjunction with an ECG telephone transmitter, telephone amplifier, and ECG recorder to form a telemetry system capable of ECG monitoring.

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Artifacts in portable electrocardiographic monitoring

A Z Krasnow
D K Bloomfield M D *
Urbana Champaign Ill

This article describes a series of artifacts encountered in 466 cases of portable electrocardiographic monitoring by a technique known as dynamic electrocardiography (DCG) Although standard 12 lead electrocardiographic artifacts have been documented repeatedly there have been only scattered reports of DCG artifacts and physicians are generally less familiar with their characteristics Since artifacts always enhance the possibility of improper diagnosis which leads to improper therapy we believe that our experience will be useful to those who use portable ECG monitoring techniques

Methods

The equipment used in these studies was the Avionics Model 350 Electrocardiocorder and the Avionics Model 650 Composite Electrocardioscanner Patients were unselected individuals who were referred for monitoring by their private physicians the patients complaints were varied the most prominent being chest pain palpitations and dizziness–syncope Subjects ranged in age from 14 to [illegible] years Some patients were ambulatory at home work or within a hospital others were at bed rest Electrodes were positioned with the exploring electrode at the V_5 position and the reference electrode over the manubrium

All tapes were scanned by a single technician who printed out suspicious areas of the recording No effort was made to quantify the incidence of specific artifacts except in general terms of rare occasional or common

Results

Artifacts discovered were divided into two general categories pseudo arrhythmias and non arrhythmias A classification of the artifacts their relative frequency probable cause and potential seriousness is shown in Table I Some were trivial whereas others created serious problems in interpretation and in two instances almost caused the unnecessary implantation of an artificial cardiac pacemaker

Pseudo arrhythmias mimicking supraventricular rhythms are shown in Figs 1 2 and 3 Fig 1 shows pseudo premature atrial contractions They are identified as an artifactual intermittent slowing of the recorder for brief periods with normal operation thereafter The complexes appear smaller and compressed in time as if there were a transient excess load placed on the battery driven mechanism That this was not due to battery failure per se is seen by the fact that tracing *a* of Fig 1 shows the same artifact recorded 9 hours before tracing *b* in which the artifact continues the same battery was in continuous use Replacement of the Electrocardiocorder motor eliminated the artifact The Fig 1 artifact might also be interpreted as pseudo premature junctional beats since the P wave is distorted and the P R interval is reduced to less than 0 12 second

Fig [illegible] pseudo sinus or atrial tachycardia is a relatively common artifact associated with battery or electric motor failure and has been described by others Characteristically it appears toward the end of the recording tape is of gradual onset and is accompanied by gradual

From the University of Illinois College of Medicine School of Basic Medical Sciences Urbana-Champaign Ill

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Reprint requests D K. Bloomfield M D Medical Sciences Bldg., Urbana, Ill. 61801

*Dean University of Illinois, College of Medicine School of Basic Medical Sciences.

Table I Classification of artifacts

Type of artifact	*Figure number in text*	*Relative frequency*	*Probable cause*	*Potential effect on diagnosis and treatment*
1 Pseudo arrhythmia				
a Supraventricular				
1 Pseudo-PAC	1	Occasional	A	Possible
2 Pseudo-PAT	2	Occasional	B	Serious
3 Pseudo-atrial fibrillation	3	Rare	U 1	Serious
b Ventricular				
1 Pseudo-PVC	4	Occasional	C 1	Possible
2 Pseudo-fusion beat	5	Common	C 1	Minimal
3 Pseudo-ventricular tachycardia	6	Rare	U 2	Serious
c Junctional or dissociative				
1 Pseudo-junctional rhythm	7	Rare	A	Possible
2 Pseudo-Mobitz II A V block	8	Occasional	C 1	Serious
3 Pseudo-sinus arrest	9	Rare	D	Serious
2 Non arrhythmia				
a Voltage or frequency response disturbance				
1 Pseudo alternancy	10	Occasional	C 1	Minimal
2 Pseudo-low voltage	11	Occasional	E	Minimal
b Tape and polarity reversal				
1 Tape reversal	12	Occasional	F	Serious
2 Polarity reversal	13	Occasional	F	Serious
c Pseudo alternans ("Siamese twins")	14	Rare	F	Possible
d Alteration of QRST (pseudo-primary T wave changes)	15	Common	C 2	Serious

A Electrical or mechanical artifact of recording device cause unknown *B* Electrical artifact of recording device due to battery or electric motor failure *C 1* Body movement or disturbance of skin electrode contact *C 2* Body movement causing a change in the recording dipole *D* Mechanical artifact of playback device *F* Technician error *U 1* Unknown cause probably a loose or broken wire connection *U 2* Unknown cause probably exercise

diminution, and often cessation, of the signal The characteristics may vary depending upon whether the cause is a loss of battery charge or a motor which draws excessive current the former being of shorter duration before complete loss of signal

Fig 3 shows pseudo atrial fibrillation probably associated with a loose connection or broken lead [18] Parts of the tracing (Fig 3 *a*) might be confused with Parkinsonian tremor, but this was not consistent throughout Fig 3 *b* shows a brief period without artifact, revealing the basic sinus rhythm The premature ventricular systole at beat No 7 of Fig 3 *a* also suggests that these strips are artifactual since it has a full and exact compensatory pause unusual in atrial fibrillation

Pseudo ventricular arrhythmias are shown in Figs 4, 5, and 6 Fig 4 is an example of a pseudo premature ventricular contraction probably due to jostling of an electrode It shows basically a sinus rhythm with mild sinus arrhythmia Base line disturbances are present through the first four beats Beat No 3 is an artifactual distortion of a normally conducted beat because (1) Despite the marked QRS distortion there is no secondary T wave change (2) The T T interval between beats No 2 and No 3 shows only a 0 04 second shortening well within the sinus arrhythmia variation (3) The S wave of beat No 3 can be identified as a normal segment of the otherwise distorted QRS Its timing in relation to preceding and following S waves is well within the sinus arrhythmia limits (4) The S T segment following the S wave like the T wave has normal configuration

Fig 5 shows a pseudo fusion beat The complex is characterized by a sudden loss of frequency response noted in both the P wave and the QRS complex Electrical recovery is not entirely complete until the second beat after the pseudo fusion beat For a period of 0 24 second before the aberrant QRS to immediately thereafter, there is a high frequency cut off disturbance which

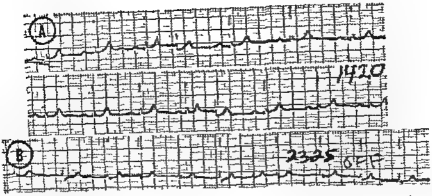


Fig 1 Pseudo-atrial or pseudo junctional premature contractions associated with Electrocardiocorder battery failure

distorts the baseline the P wave and the QRS The baseline throughout the strip shows small high frequency irregularities except during the period in question The 50 per cent reduction in QRS voltage occurs toward the end of the artifactual period and it is likely that the peak of the artifactual disturbance obliterated the normal P wave The artifact is probably caused by some type of electromechanical disturbance affecting the frequency response of the recorder It is an incomplete form of the artifacts seen in Fig 8

Fig 6 a continuous strip is a dramatic example of pseudoventricular tachycardia cause unknown The initial sinus rhythm is noted to be gradually engulfed by an undulating artifact which gradually poses as a ventricular tachycardia The R R interval of the normal QRS complexes can be followed throughout as indicated by the time intervals noted on top of the strips Toward the end of the episode (Fig 6 *d*) the QRS complexes can be identified as the process concludes

Several artifacts (Figs 7 8 and 9) mimicked junctional rhythm and conduction or pacemaker disturbances Fig 7 is really an example of a frequency response disturbance simulating a junctional rhythm Fig 8 shows two extreme examples of temporary impairment of electrode contact posing as advanced A V block The blocked P wave in Fig 8 *a* is actually a diminutive QRS complex since it is not synchronized with the preceding P wave and is of a different configuration The P wave preceding and the T wave following that complex are completely lost

Figs 8 *b* and *c* come from a different patient

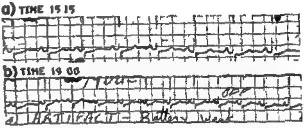


Fig 2 Pseudo sinus or atrial tachycardia due to battery failure At 15 15 (*a*) the record shows normal sinus rhythm at a rate of 94 per minute At 19 00 (*b*) the artifactual rate is 144 but there is compression of the entire PQRST complex including a loss of voltage

whose electrocardiogram showed atrial fibrillation and left bundle branch block Tracing *b* was originally interpreted as a reversion to normal sinus rhythm with advanced A V block requiring pacemaker insertion This was in error because the complexes masquerading as P waves are irregular and are actually compressed QRS complexes reflecting normally conducted beats in the presence of atrial fibrillation

Fig 9 shows unusual artifacts related to the playback process They resulted when the company which manufactured the recording tape (3 M Company – 200 Tape) discontinued its line and replaced it with a new product (178 Tape) to give higher recording fidelity The result was not a success for the DCG method The new tape tended to adhere to the slow speed scanning head of the Electrocardioscanner The combination of the tape slowing with the strip chart recorder running at 25 mm per second produced the effects seen in Fig 9 In each instance the slowing or temporary stoppage of the tape caused by its

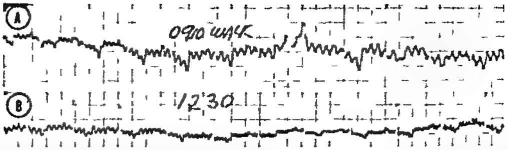


Fig 3 Pseudo atrial fibrillation The artifact persisted throughout the recording except for brief periods of clarity (*b*) The patient did not suffer from Parkinson's disease or have any other observable tremor A 12 lead electrocardiogram was free of artifact (time interval in seconds)

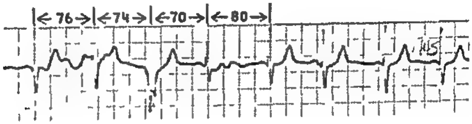


Fig 4 A pseudo premature ventricular contraction The aberrant complex appears to be premature but it is an artifact obscuring a normal QRS which can be identified by its relatively normal S wave S T segment and T wave (time intervals in seconds)

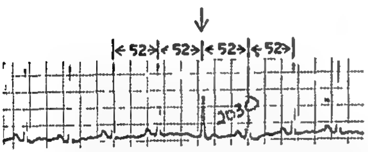


Fig 5 Pseudo fusion beat The designated complex is an incomplete form of the examples shown in Fig 8 Note the change in P wave configuration preceding the complex (time interval in seconds)

sticking to the scanning head produced artifacts that resembled either marked sinus arrhythmia bradycardia or sinus arrest In some instances the artifact is readily identified by the obvious broadening of the total PQRST complex (Fig 9 *b*) but this was not always possible since the stoppage occasionally occurred abruptly between complexes (Fig 9 *a*) When the tape was released the recording of normal sinus rhythm reappeared Misinterpretation of these artifacts has also led to the improper recommendation of insertion of a cardiac pacemaker

Several artifacts were noted that did not fall into the category of pseudo arrhythmias Fig 10 is closely related to Figs 2 and 8 The complexes seem to be similar to aberrant QRS conduction seen commonly with atrial premature contractions Fig 11 relates to the battery failure noted in Fig 2 except that the dominant effect is loss of signal The loss of signal has obliterated the P waves so that any atrial arrhythmia would be difficult to diagnose For example the loss of P wave signal in the presence of sinus arrhythmia could lead to the erroneous diagnosis of atrial fibrillation

Occasionally, the technician confuses the beginning and the end of the tape so that the DCG printout appears as a mirror image (Fig 12) The reversal is simple to identify in Fig 12 a but when the T waves are less prominent (Fig 12, *b*) the reversal may go unnoticed Failure to identify the reversal can lead to the diagnosis of a misleading Q wave This was particularly evident from a second case Fig 12 c in which the broad S waves of an episode of paroxysmal atrial tachycardia appear as broad Q waves suggestive of myocardial damage

Similar problems can arise if the recording electrodes are transposed leading to polarity reversal (Fig 13) This is usually evident but again misleading Q waves can be seen

A most interesting artifact and one previously reported,[10, 11] is the presence of a double imprint on the recording tape Fig 14 is an example of two independent rhythms on a single tape which

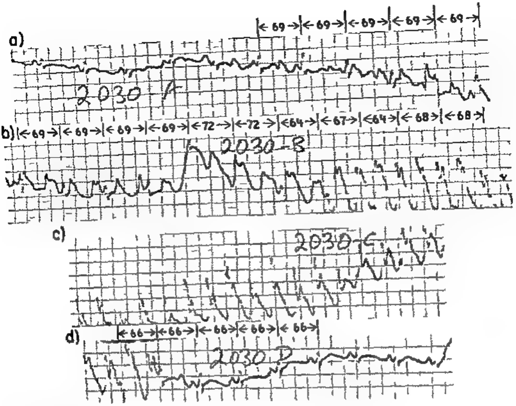


Fig 6 Pseudo ventricular tachycardia The cause of the rhythmic artifact is unknown but the normal QRS complexes can be followed throughout most of the tracing (The tracing is a continuous strip R R intervals are noted in seconds)

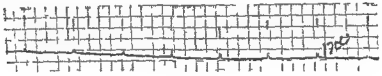


Fig 7 Pseudo junctional rhythm This is an example of a low frequency cut off disturbance of the recording equipment

could easily be mistaken as a sign of serious heart disease manifested as electrical alternans The independence of the rhythms is evident by noting that the coupling interval between the large and the small complexes is constantly changing indicating two independent rates At the beginning of the strip the small complex appears coupled to the large one whereas at the end of the strip the reverse is true The tracing appears to be from two separate individuals and indeed we have seen similar tracings from Siamese twins The most likely cause of this artifact is the re use of an incompletely erased tape Although we did not knowingly re use tapes this could have happened inadvertently It is also possible that the artifact could have been caused by a particularly strong signal imprint affecting adjacent sections of the thin 0 5 mil tape wound upon the spool In any event it can be identified as an artifact by its parasystolic nature It is differentiated from true parasystole by its complete independence from refractory periods

A final artifact one that is perhaps the most difficult to deal with is the change in complex configuration associated with body movement or position An example is seen in Fig 15 in which apparent T wave inversions are recorded These T wave inversions are probably secondary to positional changes about the recording dipole It should be noted that the S wave in Fig 15 *a* is incorporated into a late slur in the R wave of tracing *b* the more prominent the S wave in Fig

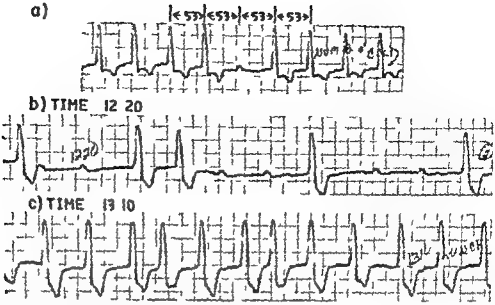


Fig 8 a Pseudo-second-degree A V block The small complex after the fourth QRS is not a P wave but is actually a normal QRS incompletely recorded (time intervals in seconds) b and c Artifactual pseudo advanced A V block in the presence of atrial fibrillation and bundle branch block

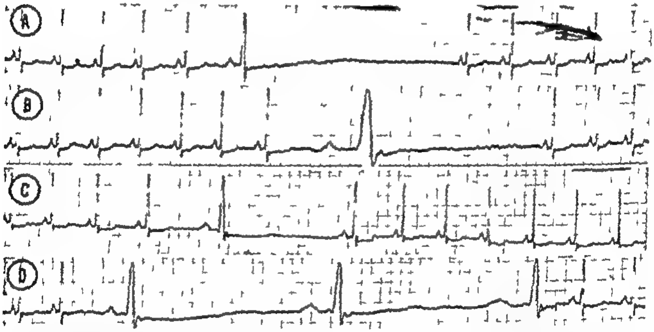


Fig 9 Four examples of pseudo sinus arrest (sinus bradycardia or arrhythmia) In example a the tape stoppage occurred between two successive complexes examples b c and d are variations of tape slowing or stoppage noted from a single patient whose basic rhythm was regular

15 the more normal' is the P wave Similarly the S T segments tend to follow the positional T wave changes These are very common findings in the records of patients who were later considered to have normal hearts as well as those with known abnormalities

Discussion

ECG interpretation has always required knowledge of and ability to recognize artifacts The same skills are required for DCG interpretation together with a new set of problems associated with battery operated equipment The early DCG reports of Gilson and associates' summarized artifactual patterns as seen by oscilloscope but pseudo arrhythmias were not described Hinkle and associates' studied the physical limitations of the DCG system and cautioned particularly against overinterpretation of S T segment and T wave changes a warning recently repea

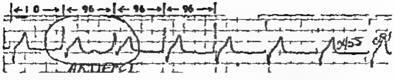


Fig 10 Pseudo-aberrancy due to a temporary change in frequency response (time intervals in seconds)

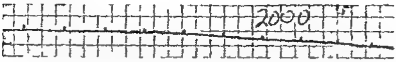


Fig 11 Pseudo low voltage and tachycardia associated with partial battery failure The changes noted are similar to those in Fig 2 but the predominant effect is a loss of voltage with less prominent development of a pseudo tachycardia

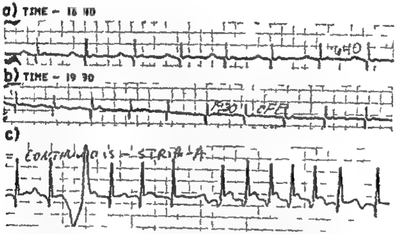


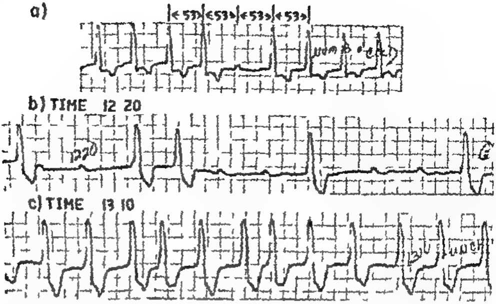
Fig 12 Two strips from a reversed tape (*a* *b*) The second strip at 19 30 suggests A V dissociation. In c a second example of tape reversal demonstrates in mirror image an episode of paroxysmal atrial tachycardia and a PVC

ed and denied Pseudo arrhythmias have been described infrequently

Aside from the intellectual challenge of identifying the arrhythmic and non arrhythmic artifacts of Table I the effect of misinterpretation can be potentially dangerous As noted in the table failure to correctly identify artifacts could lead to serious consequences in [illegible] of the 15 examples Among the supraventricular pseudo arrhythmias the false sinus or atrial tachycardia could lead to unnecessary digitalization Conversely the false atrial fibrillation shown in Fig 3 with the regular R R intervals could be mistaken for a junctional rhythm in the presence of atrial fibrillation and digitalis intoxication

The pseudo-PVC s and artifactual fusion beats are relatively trivial but the pseudoventricular tachycardia of Fig 6 might lead to drastic and unnecessary measures The pseudo arrhythmias seen in both Figs 8 and 9 could be interpreted as indicating a need for the implantation of an artificial pacemaker, and in 2 cases this almost happened

The main danger presented by non arrhythmic artifacts is the tendency to overinterpret the changes The examples of tape reversal and polarity reversal (Figs 12 and 13) both demonstrate large Q waves that would ordinarily be abnormal in the V_5 electrode position More common and more important are the many ST T changes that are observed during the course of DCG monitoring The monitoring dipole lies between the manubrium and the V_5 position and is relatively sensitive to changes in body position Thus it is common to see the S waves wax and wane as in Fig 15 with associated secondary T wave changes Similarly the S T segments shown in Fig 15 change from concave upward and



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symptoms throughout the recording period some of these symptoms occurred simultaneously with ST T changes and some occurred in the absence of such changes The picture was often so con fusing that additional diagnostic tests such as exercise tolerance tests or coronary angiography were recommended

The causes of monitoring artifacts were not always obvious nor subject to proof We have indicated the probable cause in Table I omitting the most common and obvious artifacts back ground noise and baseline movement These ar tifacts can be reduced or eliminated by careful technique in preparing the skin and carefully attaching the electrodes Battery failure artifacts (Figs 2 and 11) always occur toward the end of monitoring but mechanical and movement arti facts can occur at any time The pseudo sinus arrest artifacts of Fig 9 were really a playback, rather than a recording artifact In general artifacts can be caused at any point in the monitoring sequence from the time of attachment of the electrodes until final interpretation

Summary

The development of portable ECG monitoring techniques has brought with it new insights into the electrical activity of the heart and new problems in interpretation of artifacts This article summarizes and classifies 15 different types of artifacts observed from dynamic electro cardiography The artifacts appear partly as pseudo arrhythmias mimicking supraventricular ventricular junctional and dissociative rhythms There are also non arrhythmic artifacts which can be misleading in the interpretation of Q waves S-T segments and T waves Eight of the 15 artifacts have potentially serious consequences if not understood and in 2 instances an artifact almost led to the unnecessary implantation of an artificial cardiac pacemaker

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Fig 13 Reversed polarity resulting from incorrect electrode placement

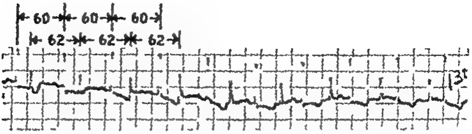

Fig 14 Pseudo-electrical alternans or the Siamese twin effect There is dissociation between the two sets of complexes (time intervals in seconds)

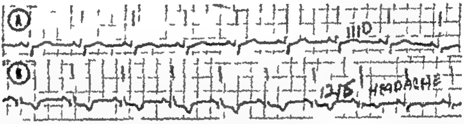

Fig 15 Positional changes which lead to an apparent change in QRST conduction and which simulate primary T wave changes These changes were present throughout the tracing T wave inversions always accompanied the loss or diminution of the S wave

isoelectric to concave downward and slightly depressed These changes also appear secondary to QRS changes associated with the variable representation of the cardiac vector on the dipole

Recently Stern and Tzivoni[14,15] challenged the work of Hinkle and associates[8] and concluded that the DCG system reliably recorded the ST T segment for the evaluation of dynamic changes induced by ischemia We cannot agree with their conclusion Although proof is lacking, we have seen numerous S T segment and T wave changes by DCG monitoring that appeared to be inconsistent with the diagnosis of ischemic heart disease It is of interest that in Fig 4 of one of Stern and Tzivoni's papers[15] the changes reported as 'deterioration of ST T changes during sleep are almost identical with our Fig 15 the T wave inversions shown being inversely proportional to the depth of the S wave Furthermore, there is a vast literature which indicates that ST T changes alone must be evaluated in terms of the physiologic status of the subject[17]

The ST T-wave changes on DCG monitoring are also greatly exaggerated in the presence of left ventricular hypertrophy and/or digitalis As with all ST T-wave changes observed by this technique, they are interpreted with extreme caution as positional artifacts unless there are compelling facts to the contrary

The diagnosis of artifacts requires, above all a high index of suspicion The only diagnostic rule we can advise is to assume that all anomalies detected by portable monitoring are artifactual until proved otherwise by careful measurements logic, or confirming diagnostic tests DCG complexes from a single pair of electrodes should always be compared to a reference 12 lead electrocardiogram Some artifacts are obvious (Figs 7, 11, and 13), whereas others are extremely subtle (Figs 6 8, and 15) The incidence of artifacts during 8 hours of recording will necessarily exceed the incidence of artifacts recorded during the 1 minute of recording represented by the standard ECG The patient's diary recording subjective symptomatology during the recording may complicate interpretation particularly with respect to subtle changes of the S T segments and T waves A number of patients who were monitored for symptoms of bizarre chest pain recorded

symptoms throughout the recording period some of these symptoms occurred simultaneously with ST T changes and some occurred in the absence of such changes The picture was often so confusing that additional diagnostic tests such as exercise tolerance tests or coronary angiography were recommended

The causes of monitoring artifacts were not always obvious nor subject to proof We have indicated the probable cause in Table I omitting the most common and obvious artifacts background noise and baseline movement These artifacts can be reduced or eliminated by careful technique in preparing the skin and carefully attaching the electrodes Battery failure artifacts (Figs 2 and 11) always occur toward the end of monitoring but mechanical and movement artifacts can occur at any time The pseudo sinus arrest artifacts of Fig 9 were really a playback rather than a recording artifact In general artifacts can be caused at any point in the monitoring sequence from the time of attachment of the electrodes until final interpretation

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Systolic time intervals in induced atrial fibrillation in the dog

Mark B Knudson, Ph D
James Amend, Ph D
Pullman Wash

The function of the atria in the dynamics of cardiac contraction has been appreciated since the observations of William Harvey, but the exact mechanisms by which atrial dysfunction may affect ventricular performance remain a subject of interest The study of uncoordinated atrial activity, such as that seen during atrial fibrillation, offers a vehicle whereby insight may be gained into the role of atrial function in the overall dynamics of the heart especially with regard to ventricular performance The realization of this goal requires definition of the relationship of atrial fibrillation to both the mechanical and the electrical function of the ventricles It also requires an appreciation of the effects of impairment of atrial and ventricular performance on cardiac efficiency This problem can be approached in a study of clinical cases of the disorder, but a more accurate definition requires the use of a controlled experimental model

The response of the ventricle itself has been studied in relation to atrial fibrillation and, whereas most early investigators felt that ventricular rate was totally irregular, Braunstein and Franke[1] observed that the ventricular rate is never totally irregular The response of ventricular rate to exercise is often inappropriate however, and one of the primary hemodynamic aberrations noted is the depressive effect of atrial fibrillation upon cardiac output[2] In the following study, a model of atrial fibrillation was used to examine some of the changes which take place in the external indicators of ventricular performance following the induction of atrial fibrillation In this manner, it is possible to gain some insight into the fundamental disruptions which occur in ventricular function following the loss of an effective atrial contribution

From the Department of Physiology and Pharmacology College of Veterinary Medicine Washington State University Pullman Wash 99163

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Reprint requests Dr Mark B Knudson Division of Animal Medicine G 602 HSC S E 20 University of Washington Seattle Wash 98195

Materials and methods

Methods Experimental subjects were 15 mongrel dogs ranging in weight from 20 to 40 kilograms Each dog was weighed and given 15 mg per kilogram of morphine sulfate subcutaneously[3] and left in a quiet area for approximately one half hour to allow the drug to exert its effect—to potentiate activity of the vagus nerve[4] At the end of the half hour period, the animal was given 3 to 5 mg per kilogram of pentobarbital sodium (Somnopentyl Pitman Moore, Inc) intravenously The animal was placed in left lateral recumbency and electrodes were positioned to record a Lead II electrocardiogram (ECG) The ECG was recorded and examined to determine the approximate cholinergic status of the atrium by observing the degree of respiratory sinus arrhythmia[5] A crystal microphone (H P 21050A) was positioned on the chest wall to record the phonocardiogram (PCG) After the microphone was in place it was manipulated until the clearest recording was obtained, with special emphasis on clear inscription of the first high frequency components of the first and second heart sounds[6] The left femoral artery was exposed and a fluid filled double lumen catheter (USCI No 5910) was inserted into the artery and connected to two Statham (Waltham, Mass) p 23ac pressure transducers The catheter was then used to introduce 50 ml of 1 0 mg per 100 ml of heparinized physiologic saline This volume was

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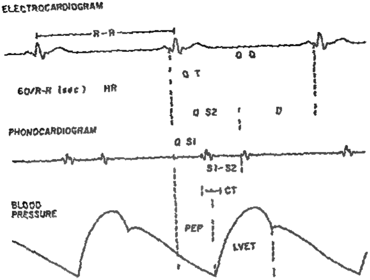

Fig 1 Measurement of the external ventricular systolic time intervals (STI) from ECG PCG and arterial pressure pulse wave records

adequate to assure heparinization of the dog The lead opening of the catheter was advanced into the left ventricle and the trailing opening was left in the root of the aorta Left ventricular pressure and aortic pressure were then measured simultaneously The external jugular vein was exposed and a bipolar recording catheter was inserted into it and advanced into the right atrium The position of the catheter was determined by noting the relative predominance of atrial electrical activity over ventricular electrical activity This determination was assisted by the simultaneous registration of a Lead II ECG The criteria used for determining catheter placement were derived from Hoff Geddes and McCrady At this time a control record was taken which involved the recording of 100 or more cardiac cycles After satisfactory control records were obtained the electrode catheter was manually manipulated with a vigorous back and forth motion for a few seconds This usually succeeded in initiating atrial fibrillation In the one case in which it did not high frequency electrical pacing for a few seconds initiated self sustaining fibrillation After fibrillation became stabilized another set of 100 or more cardiac cycles were recorded Periods of fibrillation observed in this study ranged from 5 minutes to 3 hours All recordings were made with a Grass model 7B Polygraph (Grass Instrument Co Springfield Mass)

Analysis of data The records were analyzed by first measuring the R R intervals of all cycles registered and then choosing a spectrum of 20 R R intervals which included the longest and shortest R R interval of each group (Fig 1) The R R intervals chosen were converted to theoretical heart rate by

60/R R interval (sec) = heart rate

From the selected R R intervals the following electrical parameters were measured the Q T interval corresponding to electrical systole the P R interval corresponding to conduction time through the atria and the A V node and the QRS duration corresponding to electrical excitation of the ventricles The left ventricular ejection time (LVET) was measured from the upstroke of the anacrotic limb of the arterial pressure wave form to the nadir of the dicrotic notch (Fig 1) The aortic end-diastolic pressure (AEDP) afterload was measured from the arterial pressure wave form The Q S_2 interval which corresponds to electromechanical systole was measured from a perpendicular extended from the Q wave of the ECG tracing to the onset of the initial high frequency component of the second heart sound The S S_2 interval mechanical systole was measured from the onset of the initial high frequency component of the first heart sound to the onset of the initial high frequency component of the second heart sound (Fig 1) Left ventricular end

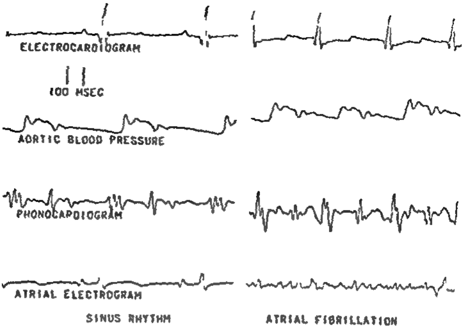

Fig 2 Typical records obtained during periods of sinus rhythm and during periods of atrial fibrillation

Table 1 Systolic time intervals during normal sinus rhythm in the dog*

Dog No	HR (b p m)	Q T (msec)	S S (msec)	Q S_1 (msec)	LVET (msec)	AEDP (mm Hg)	LVEDP† (mm Hg)	P R (msec)	QRS (msec)	Q S (msec)	LVPEP (msec)	EICT (msec)
2	68 4	265 0	210 0	305.5	205 0	5[illegible] 6	–	150 0	59 5	102 5	101 5	13 0
3	63 [illegible]	283 0	241 0	308 0	210 0	52 2	–	131 0	60 0	60 5	98 0	31 0
6	63 3	242 5	210 0	298 5	204 0	86 0	–	112 0	60 0	66 5	94 5	28 0
9	65 4	270.5	249 0	315 0	227 7	68 7	–	117 5	56 0	66 0	88 0	21 5
10	86 8	258 0	232.0	309.5	222 0	76 7	–	103 0	57 0	76 0	87 0	10 0
13	62 1	289 0	212 0	283 0	194 0	80 7	–	119 5	52 0	68 0	89 0	18 0
14	73 2	241 0	218 2	300 7	200 7	68 2	–	133 7	55 0	82 5	101 5	14 0
16	8[illegible] 1	292 1	224 4	301 7	206 5	78 0	–	122 9	58.5	77 3	97 2	19 2
18	84 3	223 5	222 7	302 3	206 7	73 0	–	139 2	49 2	79 7	94 5	15 7
19	94 0	238 0	224 0	301 0	207 0	81 7	–	102 7	62 6	75 5	93 2	16 2
22	67 6	252 6	238 7	306 0	222 0	74 5	8 8	122 1	55 5	68 7	83 5	17.2
23	[illegible] 7	238 0	232 5	305 7	213 5	77 0	8 3	125 7	57 5	73 0	92 5	19 0
24	67 3	261 2	225 0	303.5	211 0	62 2	5 5	131 2	57 5	78 5	92 5	16 0
25	68 5	278 7	231 5	303 3	211 2	62 8	9 2	129 0	69 8	71 7	91 0	20 0
26	73 6	246 2	213 0	287 5	195 0	82 0	8 4	119 0	52 5	74 7	93 0	19 2
Mean	71 8	258 6	225 6	302 1	209 1	70 6	8 0	123 9	56 2	74 7	93 1	18 8
S D	20 3	16 5	9 7	8 1	9 7	10 4	5 4	8 5	2 9	8 4	9 1	6 7
S E M	1 2	1 0	0 6	0 5	0 6	0 6	0 5	0 5	0 2	0 5	0 5	0 4

[illegible] = 300 cycles
†n = 100

diastolic pressure (LVEDP) or pre load,[7] was measured from the recording of left ventricular pressure Using these measured intervals the remaining members of the STI were calculated by the method of Weissler and associates[8] These intervals include the Q S_1 interval which constitutes electromechanical delay and is calculated by subtracting the S_1 S_2 interval from the Q S_2 interval, the left ventricular pre ejection period (LVPEP) obtained by subtracting LVET from the Q S_2 interval and the external isovolumic contraction time (EICT), derived by subtracting LVET from the S_1 S_2 interval The legitimacy of determining EICT and LVPEP in this manner, rather than by direct means, has been demonstrated by Bush[9]

In 10 dogs the AEDP was measured and in 5 dogs both AEDP and LVEDP were measured In the atrial fibrillation records determination of the fibrillation frequency was made in 5

Table II Systolic time intervals during atrial fibrillation in the dog*

Dog No	*HR* (b p m.)	*Q T* (msec)	*S S* (msec)	*Q S* (msec)	*LVET* (msec)	*AEDP* (mm Hg)	*LVEDP*† (mm. Hg)	*FF* (/ min)	*QRS* (msec)	*Q S* (msec)	*LVPEP* (msec)	*EICT* (msec)
2	61.7	301.5	240.0	3[illegible]0.5	207.5	54.0	—	1,356	62.0	80.0	113.0	32.5
3	65.7	273.0	251.0	311.0	208.5	46.5	—	1,3[illegible]6	56.0	61.0	100.0	43.0
[illegible]	60.9	239.5	240.5	300.5	205.5	79.5	—	1,294	59.7	60.0	95.0	36.0
9	71.3	2[illegible]0.5	246.0	307.0	211.0	50.5	—	1,098	56.0	61.0	96.0	35.0
10	74.2	264.0	236.0	299.0	20[illegible].0	58.0	—	1,154	50.2	75.0	98.1	34.0
13	83.7	268.0	226.0	287.0	182.0	67.2	—	705	50.0	62.0	106.0	45.0
[illegible]	[illegible]9.6	23[illegible].6	228.5	298.5	192.0	47.2	—	1,780	49.0	69.7	108.0	36.5
16	78.1	287.7	240.7	304.2	197.2	77.5	—	1,3[illegible]0	57.6	63.7	106.0	43.5
18	93.0	223.3	238.5	30[illegible].5	[illegible]00.7	62.[illegible]	—	1,080	48.5	64.0	101.[illegible]	37.7
19	111.7	226.3	232.2	291.2	191.0	70.[illegible]	—	1,380	51.6	59.0	101.5	41.7
22	83.1	251.5	236.5	297.7	194.0	80.0	8.2	876	58.5	61.2	102.5	42.0
23	64.7	236.2	236.5	299.0	196.5	73.0	6.0	10[illegible]0	57.5	64.0	104.0	39.5
[illegible]4	78.8	246.2	236.7	292.7	196.7	57.2	9.8	1,968	57.7	55.7	101.5	40.0
25	[illegible]8.1	2[illegible]2.7	239.2	300.0	197.5	59.0	5.5	1,295	58.5	61.7	102.5	41.7
[illegible]	88.7	[illegible]28.7	224.2	278.7	182.5	84.2	5.2	1,112	57.2	54.5	101.3	39.7
Mean	[illegible]8.2	255.1	236.8	299.3	197.6	64.4	6.9	1,251	55.4	63.5	102.4	39.2
S D	44.8	16.4	13.9	14.3	16.7	19.2	3.6	—	3.1	9.1	12.5	10.0
S E M	2.6	0.9	0.8	0.8	0.9	1.1	0.4	—	0.2	0.5	0.7	0.6

*n = 300 cycles.
†n = 100

to 10 evenly spaced areas in the record (Fig 2)

Data evaluation The measured and calculated intervals for each heart rate in individual animals were tabulated and averaged Twenty R R interval matched cardiac cycles from each condition i e control and atrial fibrillation were evaluated for each animal for a total of 40 cardiac cycles Each individual was used as its own control and compared for significant change in the STI after the induction of atrial fibrillation within itself and the STI of all individuals in one condition were compared with all individuals in the other condition by means of Student's paired t test

Results

Sinus rhythm Twenty cycles of normal sinus rhythm were examined in 15 dogs resulting in a total of 300 cycles analyzed Table I is a presentation of the mean values for all parameters from each individual dog The average instantaneous heart rate for 300 cycles was 71 8 beats per minute The Q T interval was 258 6 msec and the P R interval was 123 9 msec The QRS duration was 56 [illegible] msec The S_1 S_2 interval was 225 6 msec and the Q S_2 interval was 302 1 msec with a Q S_1 interval of 74 7 msec

The mean left ventricular ejection time (LVET) was 209 1 msec. with an aortic end diastolic pressure (AEDP) of 70 6 mm Hg and a left ventricular end diastolic pressure (LVEDP) of 8 0 mm Hg For the pre-ejection phenomena left ventricular pre ejection period (LVPEP) was 93 1 msec and the externally derived isovolumic contraction time (EICT) was 18 8 msec

Atrial fibrillation The same 15 dogs used in the evaluation of the sinus rhythm parameters were evaluated after atrial fibrillation was induced Twenty cycles were examined for the same parameters as were evaluated during sinus rhythm in each dog with a total of 300 cycles examined (Table II) The average instantaneous heart rate for these 300 cycles was 78 2 b p m The Q T interval was 255 1 msec with QRS duration of 55 4 msec The mean fibrillation frequency (FF) was 1 251 per minute The S_1 S_2 interval was 236 8 msec the Q S_2 interval was 299 3 msec and the Q S interval was 63 5 msec (Table II)

The mean LVET was 197 6 msec with an AEDP of 64 4 mm Hg and a LVEDP of 6 9 mm Hg The LVPEP was 102 4 msec and the EICT and 39 2 msec

Effect of atrial fibrillation on the STI Table III shows data for the parameters which were not significantly affected by the induction of atrial fibrillation These include the average instantaneous heart rate which, although marginally increased was not significantly affected Total

Table III Values for parameters which were relatively unaffected by the induction of atrial fibrillation in the dog*

Experimental conditions	*HR (b p m)*	*Q T (msec)*	*Q S (msec)*	*LVEDP† (mm Hg)*	*AEDP (mm. Hg)*	*QRS (msec.)*
Sinus rhythm	71.8 ± 1.2	258.6 ± 0.9	302.1 ± 0.5	8.0 ± 0.5	70.6 ± 0.6	56.2 ± 0.2
Atrial fibrillation	78.2 ± 2.6	255.1 ± 0.9	299.3 ± 0.8	6.9 ± 0.4	64.4 ± 1.1	55.4 ± 0.2

*Values expressed as mean ± S E M., n = 300 cycles for each condition
†n = 100
p < 0.001

Table IV Values for parameters which were affected by atrial fibrillation in the dog*

Experimental conditions	*$S_1 S_2$ (msec)*	*LVET (msec)*	*Q S (msec)*	*LVPEP (msec)*	*FICT (msec)*
Sinus rhythm	225.[illegible] ± 0.6	209.1 ± 0.6	[illegible]4.7 ± 0.5	93.1 ± 0.5	18.8 ± 0.4
Atrial fibrillation	236.8 ± 0.8	197.6 ± 0.9	63.[illegible] ± 0.5	102.4 ± 0.7	39.2 ± 0.6

Values expressed as mean ± S E M n = 300 cycles for each condition
p < 0.001

ventricular electrical systole (Q T interval) was unaffected, the same was true of electromechanical systole (Q S_2 interval) and the ventricular electrical activation time (QRS duration) LVEDP and AEDP were not significantly reduced

As indicated in Table IV, there was a significant increase in the duration of mechanical systole ($S_1 S_2$ interval) following induction of atrial fibrillation, with a significant decrease in the duration of both LVET and the electromechanical delay (Q S_1 interval)

Of all the STI measured the pre ejection phenomena were the most profoundly affected by the induction of atrial fibrillation with a dramatic increase in both the LVPEP and EICT

Discussion and conclusions

In clinical studies in humans with atrial fibrillation, the ventricular rate is often found to be very rapid (An exception to this is seen in cases in which there is disruption of the electrical activating system in the ventricles)[9] In studies reported here, a cyclically irregular heart rate was observed which was within the normal range for dogs[10] An explanation for this probably relates to the potentiation of vagal influences upon the A V node, with decreased conduction velocity and increased refractory period in the node thus maintaining ventricular rate relatively low in comparison to the atrial rate

The effects of atrial fibrillation on ventricular performance are multiple The physiologic basis for these changes has been the subject of a number of studies demonstrating changes in some of the common measurements of cardiac performance Halmos and Patterson[11] showed that cardiac output in human patients with atrial fibrillation is normal when they are at rest but that the increase in cardiac output is inadequate to meet tissue demands during exercise Tavel and associates[12] reported that the correlation between increasing R R interval and increased duration of LVET, which holds true in normal individuals,[13] applied only in the narrow ranges of about 50 to 100 beats per minute in patients with atrial fibrillation This is in agreement with our finding of a shortened LVET in all of the dogs after the induction of atrial fibrillation In addition our study demonstrated a marked increase in the duration of LVPEP while the Q S_2 interval remained unaffected during atrial fibrillation This observation has recently been confirmed by Lewis and co workers[14] in a prospective study of LVPEP in human patients with atrial fibrillation This change in the pre ejection phenomena is compatible with the observed decrease in LVET with an unaffected total electromechanical systole (Q S_2 interval), since total electromechan

ical systole is the sum of the pre ejection and ejection phenomena With the decrease in LVET, the pre ejection period must perforce increase if total electromechanical systole is to remain unaffected It can be demonstrated that this change in the LVPEP results primarily from an increased EICT The LVPEP was increased by 9 msec This was concomitant with a decrease of 11 msec in the electromechanical delay (Q S, interval) The 9 msec increase in the LVPEP which occurred was therefore the result of a 20 msec increase in the EICT which was partially offset by an 11 msec decrease which occurred in the other portion of the LVPEP—the electromechanical delay The same line of reasoning applies to the change in total mechanical systole without change in the total electromechanical systole Total mechanical systole increased by 11 msec and LVPEP increased by 9 msec which correspond well to the observed decreases in electromechanical delay and LVET of 11 and 12 msec respectively These findings indicate that myocardial contractility is reduced during atrial fibrillation

Two possible explanations for the increase in EICT are (1) a Frank Starling effect upon myocardial contractility and (2) an early closure of the A V valves The possibility that the increased EICT is the result of a decreased myocardial contractility mediated through LVEDP-dependent changes in fiber stretch and a resultant Frank Starling type effect is ruled out by the demonstration that the pre load (LVEDP) is essentially unchanged by the onset of atrial fibrillation As mentioned above a second possibility which may result in an increased EICT is an early closure of the A V valves This possibility is unlikely because the primary force involved in A V valve closure is the rapid fall in atrial pressure compared to ventricular pressure at the end of atrial systole and before the onset of ventricular contraction [18] If the valves have any effect on pre-ejection phenomena during atrial fibrillation it should be to increase the Q S interval and shorten the EICT due to the elimination of effective atrial systole In fact the magnitude of change found in the EICT is such that it cannot be explained on the basis of a decrease in the Q S_1 interval alone

In the evaluation of atrial fibrillation and its effects on cardiac performance the parameter which has received the most attention is the cardiac output The studies of Mitchell and Shapiro[19] show that depression of the response of cardiac output to tissue demand is directly related to the degree of stress which is applied to the system. This is evidence albeit very indirect that myocardial contractility is compromised by atrial fibrillation through some direct mechanism or through a reduction of diastolic filling time at higher ventricular rates

This study demonstrated a pronounced effect of atrial fibrillation on the pre-ejection phenomena with the strongest effects manifested during the phase of ventricular contraction involving the development of pressure in the ventricles against an increasing resistance—the EICT As mentioned earlier it does not appear that a Frank Starling effect or A V valve closure effects can account for the increased duration of EICT observed during atrial fibrillation

Apart from discussion concerning the mechanism for the changes seen in hemodynamic function in the presence of atrial fibrillation the definitive observation of this study is the effect of atrial fibrillation on pre-ejection phenomena in the left ventricle Its effect is also seen in the ejection phase of the cardiac cycle as indicated by the reduced LVET found in this and other studies [8] Of the pre-ejection phenomena the ability of the ventricles to develop pressure against an increasing resistance is the most seriously compromised

Summary

The effect of induced atrial fibrillation on ventricular performance in the dog as measured by changes in the systolic time intervals (STI) was investigated

Atrial fibrillation was induced by enhancement of vagal tone with morphine sulfate followed by direct mechanical stimulation of the atrium Dogs received 15 mg per kilogram of morphine sulfate subcutaneously followed by 3 mg per kilogram of pentobarbital sodium ECG, atrial electrogram, phonocardiogram and direct arterial blood pressure were recorded during periods of sinus rhythm and during periods of induced atrial fibrillation Data were analyzed by selecting 20 representative cardiac cycles from each condition in each of 15 dogs Cycles were selected so that the broadest spectrum of rates was examined for each

animal Three hundred cycles were examined from each condition, or a total of 600 cycles Heart rate (HR), left ventricular end diastolic pressure, and aortic end diastolic pressure were unchanged during atrial fibrillation The left ventricular pre ejection period (LVPEP), externally derived isovolumic contraction time (EICT) and total mechanical systole (S_1 S_2 interval) were all found to increase significantly in duration after the induction of atrial fibrillation The left ventricular ejection time (LVET) and the electromechanical delay (Q S_1 interval) were significantly decreased in duration following the induction of atrial fibrillation

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Case reports

Acute myocardial infarction following wasp sting

Report of two cases and critical survey of the literature

Harold D Levine M D
Boston Mass

In late August 1972, I examined in consultation a 39 year old man without known antecedent heart disease for acute myocardial infarction This followed a bout of generalized urticaria associated with severe hypotension collapse and cyanosis after he was stung by numerous yellow jackets A 66-year old gardener seen in consultation by a confrère only two days earlier for a similar reason likewise had had no previous experience with coronary artery disease He was quite knowledgeable about hymenoptera and declared that it was by hornets that he had been stung Well aware of the danger in the sting each patient rushed to the emergency ward of the nearest general hospital In each instance a period of collapse hypotension and cyanosis lasting at least a half hour followed multiple stings and preceded the onset of severe chest pain and the succeeding demonstration of the classical electrocardiographic sequence of acute myocardial infarction

Case reports

Case 1 H F a 39 year-old executive while working in the back yard of his home at about 5 45 P M Aug 19 1972 was suddenly seized upon by yellow jackets and stung on the scalp and in six or seven places on the legs Knowing his vulnerability to stings, his wife drove him at breakneck speed the few miles to the emergency room of the Lawrence General Hospital. En route he removed one of the wasps from his clothes, felt his tongue enlarging, and became more and more short of breath. By the time of arrival some fifteen minutes later he was unconscious and his blood pressure unobtainable. His first attendant nurse thinking that he had had a heart attack and not aware that he had been stung recorded an electrocardiogram (Fig. 1 *B*) This was within normal limits. At 5 56 P M he was given 0.5 c c of *epinephrine* subcutaneously This was repeated at 6 09 P.M He was then given 40 mg. of Solu Medrol by intravenous drip From 6 15 to 6 30 P M he had a severe shaking chill, pain in his joints and his wife noticed that his fingertips became blue Half or three-quarters of an hour later for the first time he experienced a severe pressure pain across the chest and in the shoulders broke out in a profuse sweat, and became incontinent. His blood pressure was then 92/70 At about 8 P.M he was transferred to the intensive-care unit. About twenty minutes later elevation of the RS T segments and arrhythmias including sinus arrhythmia (or sino-atrial block) and ventricular premature beats were first noticed on the monitoring screen (Fig 2) The second complete electrocardiogram recorded at about 9 30 P M (Fig 1 C) showed changes diagnostic of an acute anteroseptal myocardial infarction and the patient was transferred to the coronary-care unit His blood pressure was then 150/65 His further hospital course was quite uneventful. The early ventricular irritability disappeared following lidocaine therapy An electrocardiogram performed on Aug [illegible] 1972 (Fig 1 *D*) showed a return of the RS-T segments toward the isoelectric line and late inversion of the T waves A tracing taken on Sept 5 showed more widespread inversion of the T waves but some persistent elevation of the RS T segments (Fig 1 *E*) Fluoroscopy performed shortly before discharge showed a ventricular bulge on systole compatible with a ventricular aneurysm

When re-examined on Oct 4 1973 he reported two bouts of dyspnea and for the first time on one or two occasions, tightness in the chest on exertion Examination was not remarkable The electrocardiogram was quite like that recorded on Sept. 5 1972 (Fig 1 *E*) On Oct 30 he noticed during trying domestic situations the same intermittent sense of tightness or heaviness. On examination he showed an S3 gallop his electrocardiogram was unchanged Scratch tests with a mixed stinging insects extract were positive in a dilution of 1 100 but not in weaker dilutions Intradermal test with 1 1 000 000 dilution of the same extract was negative He was given 0 05 c.c of the same dilution subcutaneously and it was planned to continue with weekly increasing doses in the effort to immunize him. He was given a "stinging insect first aid treatment kit and told to carry it with him at all times He had been stung by a single wasp in June 1972 and

From the Departments of Medicine Peter Bent Brigham and Robert Breck Brigham Hospitals, and Harvard Medical School, Boston

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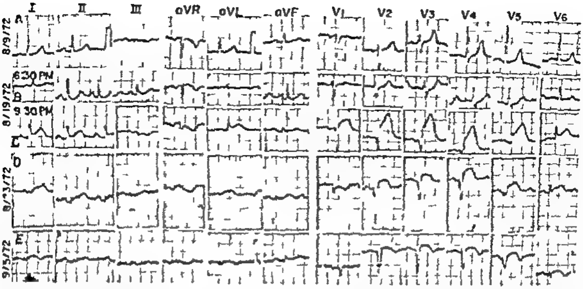

Fig 1 Case 1 acute anteroseptal myocardial infarct following sting of yellow jackets *A* normal tracings recorded *at annual check up on Aug 9 1972 B substantially unchanged tracings recorded on admission to the emergency* room on Aug 19 1972 minimal but unimpressive depression of RS T segments in Leads V V and V_4 *C* tracings recorded three hours later showing changes decisive of early anteroseptal infarct *D* tracings four days later showing sequential changes of acute transmural infarction *E* Twelve days later T waves show late inversion but RS-T segments are still somewhat elevated

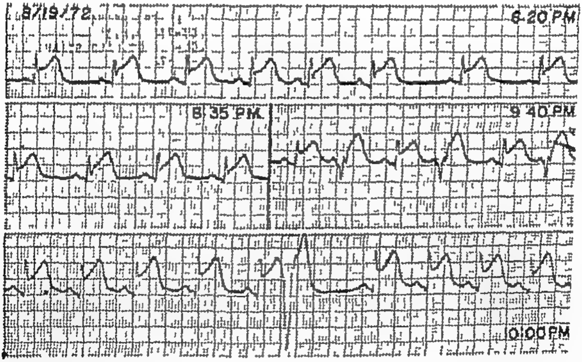

Fig 2 Case 1 strips recorded on monitoring screen between Figs 1 *B* and 1 *D* showing sinus arrhythmia (or sinoatrial block) at 8 20 and 8 35 P M ventricular premature beats at 9 40 and 10 00 P M Pronounced RS T segment elevation throughout Prominent Q waves best seen in premature beats

developed a red itching local swelling which measured six to seven inches in diameter *and lasted about a week An* annual check up had been done on Aug 9 1972 An electrocardiogram taken at that time (Fig 1 *A*) was normal The patient was advised *to lose twenty* pounds was cautioned of the danger of bee stings and advised to submit to a program of desensitization

As a boy of fourteen or fifteen he had been bitten by a thick furry bodied multicolored caterpillar *following which he* developed severe urticaria He was effectively treated for this *with gamma globulin Though he had previously been stung* by bees many times without reaction he was warned at that time that he was very sensitive to insect bites

Case 2 While clipping bushes on Aug 21 1972 C W a 66-year old gardener with Parkinson s disease *but without overt* antecedent heart disease was stung by about fifteen hornets He remained in the yard for twenty to thirty minutes was *then taken to the accident floor of the* Quincy City Hospital

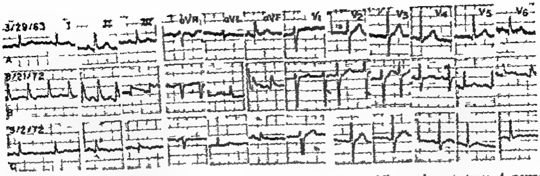

Fig 3 Case 2 acute diaphragmatic infarct and transient atrial fibrillation following hornet stings. *A* normal tracings recorded in 1963 identical with second (unreproduced) control tracing recorded in January 1972 *B* tracings recorded on the day after admission showing atrial fibrillation and elevated RS-T segments in Leads III aV_F, and V *C* twelve days later showing return to normal sinus rhythm with slight RS-T elevation in Leads II III and aV_F and more prominent Q waves in Lead III

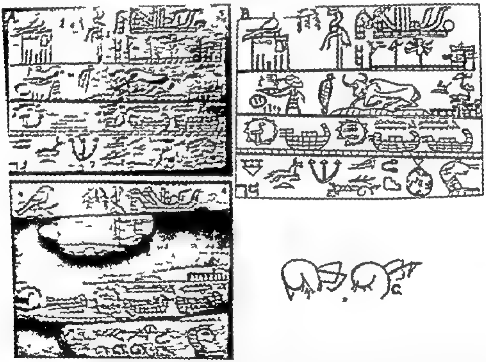

Fig 4 Anaphylactic shock, presumptive from hornet sting 2641 B C Great Ebony label from Menes tomb at Abydos *A* photographs by Sir F Petrie *B* Drawing from same by L. A Waddell and *C* detail of "fatal fly" on Menes label identified as wasp or hornet The figures in C are drawings by Waddell from lowermost panel in *A* (Reproduced from reference No 5 by permission of Luzac and Co London)

where he arrived within fifteen to twenty minutes On arrival he was unconscious and showed a diffuse itching, urticarial eruption particularly on the arms and legs and at the sites of the stings. His fingers were purple and cold and the joints of his fingers and toes were swollen He vomited twice and was incontinent of urine and feces. His blood pressure was 85 systolic 60 diastolic his heart rate was rapid at times regular at other times irregular He was given epinephrine 0.3 mg in 10 c.c of normal salt solution by vein diphenhydramine hydrochloride (Benadryl) 50 mg intramuscularly and then an intravenous drip of 1.5 Gm of aminophyllin in 1 000 c c of dextrose in water The epinephrine was repeated in the same dose and by the same route every twenty minutes for three doses The patient revived about a half hour after these measures were started He then for the first time complained of pain in the chest This lasted about two hours An electrocardiogram now showed paroxysmal atrial fibrillation and changes very suggestive of early diaphragmatic or inferola

teral myocardial infarction (Fig 3 B) These changes were in distinct contrast to two normal sets of tracings each recorded at the Quincy City Hospital the first in 1963 (Fig 3 A) when he was treated for pneumonia the second in January 1972 On the day after admission the electrocardiogram showed changes distinctive of acute diaphragmatic infarction Following this he demonstrated classical sequential changes of acute inferolateral infarct The serum transaminase (SGOT) attained a maximal level of 128 units (normal less than 40) and the creatine phosphokinase (CPK) 130 units (normal less than 60) on the second hospital day He had been stung on many previous occasions and was considered to be allergic to bees and wasps

On the initial therapy outlined above followed by two successive intravenous infusions of 100 mg of hydrocortisone and over the ensuing three days Medrol 4 mg every six hours his blood pressure rose to 130/70 and remained in that range Thereon he had an uncomplicated clinical course and has done very well since discharge He quit his work as a gardener continued for a time as a hospital employee then retired He has had no angina pectoris since his bout of acute myocardial infarction

Discussion

In every day usage a bee sting means the sting of any one of the hymenoptera Even among physicians the word "bee is commonly used in this generic sense The yellow jacket, it must be said, is not a bee Like the hornet, it is a vespine wasp[1,2] The testimony of most laymen on the identity of a biting insect is even more unreliable entomologically As emphasized by Mueller[3] when a person especially a child, even if properly taught is stung for a second time the question whether the stinging insect had a truncated or petiolate abdomen or a face with an extended oculomalar space assumes little more than academic importance Frazier[1] considered a more precise identification both desirable and feasible

Accounts of fatalities following the sting of hymenoptera date well back into antiquity Brown[4] tells of Menes navigator son of Sargon the Great who about 2641 B C was stung by a hornet while exploring the Land of the End of the Sunset'—allegedly Erin—and died almost immediately[5] (Fig 4) The Talmud tells of a Galilean who consented to lecture upon an esoteric and, to him forbidden subject whereupon 'a wasp came out of the wall and stung him and he died'[6] If these fatalities followed immediately after the sting as is implied in these accounts but not clearly stated, their mechanism could differ from that of the present two survivors

Death may occur immediately[7]—before the subject recovers from shock—or it may be delayed, and the delay may be brief or protracted[8,10] Reactions of this sort have been recorded when the sting is single or multiple[9,11] Those deaths occurring during the period of unconsciousness are now regarded as the result of anaphylaxis or, more specifically, of anaphylactic shock In those individuals who recover, anaphylaxis may be demonstrated to the hymenoptera or their venoms[12,17] Those fatalities which occur later may result not from the general effect of shock as such but perhaps from specific local effects (*Vide infra*) In the fatal case of myocardial infarction described by Berlin[14] and in each of the two surviving individuals described here a hypotensive interval followed the sting before the patient was seized with chest pain and experienced the classical sequence of events denoting acute myocardial infarction

Death from anaphylactic shock, in general, is said to occur within a half hour,[15] from insect stings to within an hour[16] Five out of six deaths from systemic anaphylaxis reported by James and Austen[8] occurred within an hour after the parenteral injection of antigen The only patient in that group who died after bee stings was found dead twenty minutes after being stung In all but one of these cases the authors adduced evidence of an anaphylactic reaction involving the respiratory tract A sixth patient died about two hours after the injection of penicillin and streptomycin, here the authors suspected a nonrespiratory possibly cardiac mechanism for this was the only patient in the group with chest pain and arrhythmia

In each of the patients described in the present report, a definite interval—a half or three quarters of an hour in the first, over an hour in the second—elapsed between sting and chest pain During this period each patient went into a state of shock and received one or more injections of epinephrine Thus the ensuing myocardial infarctions could conceivably be the effects, not of the wasp stings as such but of intervening circumstances

(1) *Anaphylactic shock* Anaphylactic reactions in general are associated with laryngeal edema, bronchospasm and severe hypotension Alone or in combination, these can lead to hypoxia general and local It is known furthermore that shock and the hypotension with which it manifests itself however induced, may lead to

Table I Anaphylaxis in relation to the heart

Authors	Reference No	Year	Species	Procedure	Observations
Auer	26	1910	Guinea pig Dog Rabbit	Anaphylactic shock Anaphylactic shock Anaphylactic shock	Bronchoconstriction Vasoconstrictor paralysis bowel. Cardiac involvement.
Auer and Robinson	27	1913	Rabbit	Anaphylactic shock	Atrioventricular block changes in RS-T and T none in QRS
Criep	29	1931	Guinea pig	Artificial asphyxia	Bradycardia partial or complete A V block 'high take-off' RS-T atrial and ventricular fibrillation
Weiss, Robb and Ellis	31	1932	Man	Injection histamine	Flattening or inversion of T waves.
Wilcox and Andrus	28	1938	Isolated sensitized guinea pig heart	Exposure to horse serum antigen	Tachycardia decrease in coronary flow and in amplitude of contraction prolongation of P R changes in QRS and T ectopic rhythms
Blumgart Schlesinger and Zoll	21	1941	Man	Injection type VIII pneumococcus antiserum	Four doses each followed by squeezing chest pain fifth by sudden death. Post mortem old and fresh infarctions
Boas	3?	1942	Man	Clinical observation Injection tetanus antitoxin Injection typhoid vaccine	Cardiac infarction followed each.
Castberg and Schwartz	30	1946-1947	Man	Injection mixed pollens (allergic shock)	ECG regarded as typical of anoxemia of heart no evidence suggesting specific allergic reaction in heart
Foster and Layman	34	1952	Man	Cinchophen plus smallpox vaccine Complained of chest pain after admission	Urticaria complete heart block, and ECG of acute diaphragmatic infarct (diagnosis rejected by authors because of rapid return of ECG to normal)
Bengtsen and Pejme	33	1952	Man	Injection tetanus antitoxin	Six days "serum sickness" Eight days weight" in chest fall in BP leukocytosis elevated ESR unstable ECG interpreted as consistent with acute anterior infarct (alternative explanation pericarditis)
LeComte	35	1957	Man	Endogenous histamine	Retrosternal oppression
James and Austen	?0	1964	Man	Injection penicillin and streptomycin	Severe chest pain cough and collapse several minutes after injection Died two hours after injection Postmortem subendocardial mottling near apex left ventricle (? due to terminal massage) Perivascular fibrosis and focal fresh hemorrhages in myocardium.

deficient coronary irrigation and thus induce myocardial infarction

(2) *Epinephrine therapy* As the principal component of generally recommended therapy for anaphylactic shock each of these patients received for its pressor effect injections of epinephrine Some forty years ago epinephrine was recommended as a provocative test for angina pectoris From fear that it might induce severe coronary insufficiency or even myocardial infarction its use for this purpose has long since been abandoned Under certain conditions moreover epinephrine may be conducive to a hypercoagulable state allegedly one of the adaptations to stress [22,23]

Allergy and anaphylaxis in relation to the heart For at least sixty years it has been claimed that the anaphylactic state may in certain

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Accounts of fatalities following the sting of hymenoptera date well back into antiquity Brown[4] tells of Menes, navigator son of Sargon the Great who about 2641 B C was stung by a hornet while exploring the Land of the End of the Sunset '—allegedly Erin—and died almost immediately[5] (Fig 4) The Talmud tells of a Galilean who consented to lecture upon an esoteric and to him forbidden subject whereupon a wasp came out of the wall and stung him and he died [6] If these fatalities followed immediately after the sting, as is implied in these accounts but not clearly stated, their mechanism could differ from that of the present two survivors

Death may occur immediately[7]—before the subject recovers from shock—or it may be delayed, and the delay may be brief or protracted [8, 10] Reactions of this sort have been recorded when the sting is single or multiple [9, 11] Those deaths occurring during the period of unconsciousness are now regarded as the result of anaphylaxis or, more specifically of anaphylactic shock In those individuals who recover, anaphylaxis may be demonstrated to the hymenoptera or their venoms [14, 17] Those fatalities which occur later may result not from the general effect of shock as such but perhaps from specific local effects (*Vide infra*) In the fatal case of myocardial infarction described by Berlin[14] and in each of the two surviving individuals described here, a hypotensive interval followed the sting before the patient was seized with chest pain and experienced the classical sequence of events denoting acute myocardial infarction

Death from anaphylactic shock, in general is said to occur within a half hour [18] from insect stings to within an hour [19] Five out of six deaths from systemic anaphylaxis reported by James and Austen [9] occurred within an hour after the parenteral injection of antigen The only patient in that group who died after bee stings was found dead twenty minutes after being stung In all but one of these cases the authors adduced evidence of an anaphylactic reaction involving the respiratory tract A sixth patient died about two hours after the injection of penicillin and streptomycin, here the authors suspected a nonrespiratory, possibly cardiac, mechanism for this was the only patient in the group with chest pain and arrhythmia

In each of the patients described in the present report, a definite interval—a half or three quarters of an hour in the first over an hour in the second—elapsed between sting and chest pain During this period each patient went into a state of shock and received one or more injections of epinephrine Thus the ensuing myocardial infarctions could conceivably be the effects not of the wasp stings as such but of intervening circumstances

(1) *Anaphylactic shock* Anaphylactic reactions in general are associated with laryngeal edema bronchospasm and severe hypotension Alone, or in combination these can lead to hypoxia general and local It is known, further more that shock and the hypotension with which it manifests itself however induced, may lead to

Postmortem	Remarks
None	Patient survived First suggestion of allergic nature of bee sting
Pericardial effusion. Coronary arteries healthy No myocardial infarct described	
None	No evidence that heart was affected
Subepicardial hemorrhages	
Hemorrhages in subepicardium subendocardium and left bundle branch	
Survived	Clinical diagnosis made in retrospect Electrocardiograms not reproduced Very convincing for acute infarct but description subject to alternative interpretation
Survived	
Large anterior wall infarct with fibrinous pericarditis and endocardial parietal thrombosis Very little coronary arteriosclerosis	Clearcut sequence of acute fatal myocardial infarct following sting of yellow jacket
Fatty degeneration of myocardium	
Patchy atheromata in coronary arteries, severe and constricting in proximal LAD Subendocardial hemorrhages upper half of septum and adjacent posterior LV wall	Fresh infarct not described.

shock as typical of anoxemia of the heart and discounted a specific allergic reaction in the heart A patient of Blumgart Schlesinger and Zoll[11] died suddenly after the fifth injection of Type VIII pneumococcus antiserum Postmortem showed old and fresh myocardial infarctions In all of these complex reactions it is clearly difficult if not impossible to separate those effects that are due to anaphylaxis *per se* from those due to the attendant shock state to asphyxia, to hypoxia or to specific chemical or toxic substances

Cardiac effects of hymenoptera stings The literature upon this subject is presented in tabular form in Table II Jensen[14] aptly comments that physicians seem to hesitate to recognize a sting as a cause of death ascribing it rather to heart disease or some other commonly accepted cause This may in part at least explain the dearth of evidence in the literature that collapse or death following the sting of bees or wasps may result from cardiac involvement Waterhouse's[11] patient felt a constriction in his throat only a few steps after being stung by a bee Following each bee sting the 54 year old nurse reported by Noble and Halley[28] placed her hand over her heart as if in pain but no further evidence was given that her heart might have been affected Horen[5] lists among the generalized reactions to hymenoptera stings a sense of constriction in the chest Such discomfort need not denote coronary insufficiency a similar sensation may be induced among other causes by bronchospasm by obstruction from laryngeal edema or by endogenous histamine[39]

In their study of 88 fatalities from wasp sting based upon death certificates and follow up questionnaires O Connor and co workers[8] considered seven to have had previous heart attacks coronary thrombosis or myocardial infarction They felt that underlying heart disease predisposed to a fatal outcome

A search of the literature in fact brought to light only two descriptions of acute myocardial infarction following a wasp sting in which acute infarction may be regarded as at least probable The first was clinical and dealt with a patient who survived the report does not make it entirely clear that the patient actually suffered a myocardial infarction[8] The second described in some detail above[14] was clinical and confirmed at postmortem It is of medicolegal interest that in this case death was declared accidental and a 50 per cent settlement given

It has been considered that the skin respiratory tract and gut are the principal target sites for allergic reactions Harkavy[3] has long championed the proposition that cardiac muscle *per se* may participate in the sensitizing in contrast to the toxic or pharmacologic effects of the intro

Table II Cardiac effects of stings of hymenoptera*

Author	Reference	Year	Age	Sex	Clinical observations
Waterhouse	14	1914	63	M	Constriction in throat few steps after bee sting
Dyke	7	1941	44	M	Previously healthy Died 20 minutes after wasp sting
Noble and Halley	36	1941	54	F	Nurse with 15 year history of cyanosis precordial discomfort, and syncope after stings by Italian honey bees.
Wegelin	11	1948	33	M	Thirty minutes after single wasp sting dizziness, pallor vomiting sweating then cyanosis and loss of consciousness. Died 30 minutes after sting
			38	M	Collapse swelling of lips and urticaria shortly after stung by at least two bees Protein and red cells in urine Died five days after sting
Milne	39	1949	49	M	Long abnormally sensitive to wasp sting Nausea vomiting diarrhea profuse sweat agonizing band like pain around chest within ten minutes of wasp sting Rigor angioneurotic edema dyspnea, and fever followed Precordial pain lasted three days Electrocardiogram recorded seven weeks later showed sharply inverted T waves in Leads I and V_1 through V_4 regarded by the author as typical of anterior myocardial infarction
Berlin	18	1953	49	M	Stiffness of lips generalized urticaria syncope few minutes after wasp sting Palpitation after revived but ECG not recorded then Following intravenous calcium ECG was normal and showed regular rhythm
			60	M	Nausea vomiting swelling of face immediately after sting of yellow jacket Then followed dyspnea chest constriction and cold clammy skin Respirations slow deep and irregular Heart grossly irregular rate 132 ECG Atrial fibrillation ventricular premature beats right bundle branch block left axis deviation Pericardial friction rub Normal rhythm slower rate next 2 to 3 days then redeveloped atrial fibrillation Died seventh day after sting
Wey	9	1956	13 months	F	Stung by about 400 wasps Collapse cyanosis pulse hardly palpable Blood pressure unobtainable Initial improvement followed day later by vomiting tachypnea coma and death 36 hours after stung
Marshall	10	1957	52	M	Stung by at least three wasps followed promptly by pallor sweating faintness cyanosis loss of consciousness Died a little more than fifteen minutes after stings

*A number of other reports (37 38 40 41 and 42) are omitted from this tabulation because protocol was obscure ambiguous or unconvincing

species at least have cardiac repercussions (Table I) In pointing out species differences in the mechanism of death from anaphylaxis, Auer[8] noted that sudden anaphylactic death in the rabbit somehow results from cardiac involvement With the advent of the electrocardiogram and the collaboration of G Canby Robinson,[27] he demonstrated atrioventricular block and changes in the RS T segment and the T wave but no QRS changes Wilcox and Andrus[28] demonstrated in the isolated guinea pig heart certain electrocardiographic changes but no evidence of myocardial infarction Criep[29] noted similar electrocardiographic changes in the intact guinea pig Castberg and Schwartz[30] regarded the electrocardiographic changes observed in five humans with 'allergic

observations Stahnke implies that the traditional use of epinephrine may need re evaluation Similar misgivings might apply to the epinephrine treatment of bee or wasp stings as well as to that of snake or scorpion bites

Entirely aside from envenomation allergic reactions in general may be associated with the local release of specific substances at least of the slow reacting substance of anaphylaxis (SRS A) of an eosinophile chemotactic factor of anaphylaxis (ECF A) presumably a peptide and of histamine or histamine like substances The antihistamines and the corticoids have been used to combat anaphylactic shock The corticoids are not devoid of their own propensity to induce thrombogenesis But the antihistamines and corticoids are much slower in their effect than the catecholamines

In this situation one cannot help but be more alarmed by the immediate precarious state of the patient with anaphylactic shock threatened as he is with deficient coronary flow The longer this is allowed to persist the more prone he is to develop and presumably the larger the resultant extent of myocardial infarction A clinical report of two cases seen in a consultative perspective is hardly the appropriate place for a definitive statement on therapy It does seem more logical however in the predicament under discussion to reverse the shock state at any cost with the more rapidly acting substance and to take one's chances on possible long term theoretical objections to its use

Summary

Over the span of two or three days in August 1972 in two separate communities in eastern Massachusetts two men one aged 39 the other 66 each without previous overt heart disease were stung by wasps Each went into shock rapidly after an interval of over a half hour developed chest pain and later sequential electrocardiographic changes diagnostic of acute myocardial infarction Each survived each had normal electrocardiograms before the sting Though preexistent coronary artery disease can be excluded in neither the view is favored that acute myocardial infarction in each was caused by deficient coronary perfusion secondary to anaphylactic shock induced by the wasp stings

An intriguing case was just recently reported of a 62 year-old man with previous angina who developed pulmonary edema but no chest pain following wasp sting and went on to show rapidly reversed electrocardiographic changes attributable to subendocardial ischemia or infarction In a sense this sequence fills the gap as an intermediate phase between the normal and the two individuals described here who developed pain after anaphylactic shock then proceeded perhaps through this phase to develop transmural infarction

I am most grateful to Dr Harry D Kaloustian of Andover for permission to report Case 1 and to Drs. Joseph M Miller and Amnon Wachman who furnished critical clinical data obtained on that patient ten days before the stinging episode to Dr Eliot Young who examined in consultation and called my attention to the second patient and to Dr George D Davidson of Quincy for permission to report that case to Drs K. Frank Austen and Albert Sheffer for helpful criticism of the manuscript to Dr Jeremiah Evarts Greene who as an allergist saw the first patient in consultation to Dr Halla Brown for furnishing reference No 5 and to Dr Harry A Savitz for reference No 6

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duction into the body of certain substances, and that this may be manifested as angina pectoris, coronary thrombosis, or various arrhythmias This view has generally been discounted In the cases reported here too it seems more logical to ascribe the acute myocardial infarctions to deficient coronary flow due to the anaphylactic shock caused by the wasp stings It must be acknowledged however, that we simply do not yet have enough data to deny that somehow the myocardial infarctions resulted not from the severe hypotension as such, but *from a direct mediator* release effect of the anaphylactic reaction upon the target myocardium, in effect a myocardial 'hive

Chemistry of the venoms Speculation and research have concerned the precise constituent or constituents of the sting and the role of the route of injection *responsible for the reactions*, both local and systemic Is this substance in the venom itself? If so, what component or components of the venom are responsible for the reaction? If not is it a somatic component of the insect s body or stinging apparatus or a pollen which is borne by the insect? Is a systemic reaction necessarily the result of the inadvertent intravenous injection? Over the years some progress appears to have been made in answering these questions Earlier studies were concerned largely with the gross pharmacologic behavior of *the venom e g, the presence in the venom of* toxic of hemolytic, of hemorrhagic or of neurotoxic principles [10] and of histamine and with the question whether it is these substances themselves or some material elaborated in the recipient of the sting in response to the injected substance or substances that is responsible for his reaction More recently, attention has been directed to the detection in the venom of more specific chemical substances [1, 44, 45] histamine [46] serotonin (5 hydroxy tryptamine), the kinins [44] (slow reacting substance of anaphylaxis or SRS A), *acetylcholine, the polypeptides*, melittin (a "direct' hemolysin), apamin (a neurotoxin), and mastocytolytic (MCL) peptide the enzymes, hyaluronidase, phospholipase A, and phospholipase B and more recently, the catecholamines [47] *It has been stated by some observers that the* hymenoptera and snake (rattlesnake cobra viper) venoms are qualitatively similar if not quantitatively *identical* [10, 45, 48] Rocha e Silva, Beraldo, and Rosenfeld of Sao Paulo [48] have shown that bradykinin, a hypotensive and smooth muscle stimulating factor, is released from plasma globulin by snake venoms (e g that of the pit viper, *Bothrops jararaca*) and that the *purified bradykinin isolated* in this manner produces a shock like condition when injected in dose of 5 to 10 mg with a steady fall in blood pressure followed by a very slow return to the initial level They speculated that bradykinin might mediate several kinds of shock and play a part in initiating vascular thrombosis A similar kinin has been detected in *wasp* and in hornet venom [44] For a more precise discussion of the resemblances and differences of the venoms of the different hymenoptera, the interested reader is referred to the excellent survey of Haberman [45]

Shenken Tamisiea and Winter [17] consider hypersensitivity to bee sting to be caused by a *protein antigen that is part of the stinger* mechanism of the bee Indeed, extracts currently used for desensitization are made not from venom *per se* but from the body of the bee

Therapeutic considerations Reference has already been made to the possible effects of one of the catecholamines epinephrine, in precipitating angina pectoris and in accelerating a hypercoagulable state This agent is most rapid in its effect The venom of the honeybee, and more particularly the yellow jacket, contains considerable amounts of the catecholamines dopamine and *norepinephrine* [47] *It has been speculated* that these serve the purpose of speeding the distribution of other constituents of the venom to their sites of action

Hemodynamic and morphologic abnormalities have been induced in the heart and circulation of laboratory animals following the administration of various sympathomimetic amines [50-56] The release or administration of catecholamines may also be involved in the induction of cardiac arrhythmias [1] The magnitude of this *factor is* uncertain and the actual situations in which it may be invoked are so complicated that it seems too speculative at present to assign an important clinical role to these substances

Stahnke [57] found that *thermal stress* like epinephrine administration enhances the toxicity of snake and scorpion venom There are not many situations more terrifying or stressful than that of being bitten by a snake or a scorpion But, epinephrine is an integral part of accepted *therapy* for toxicity from these causes In view of his

Sudden death following intravenous sodium diphenylhydantoin

Samuel Zoneraich M D FACC
Olga Zoneraich M D
Joel Siegel M D
Stony Brook N Y

Life threatening arrhythmias may occur during treatment with many antiarrhythmic drugs[1] Only a few reports[2] have been published in the English medical literature describing death following intravenous (i v) use of diphenylhydantoin (DPH) It is the purpose of this paper to present the electrocardiographic (ECG) sequence of events following the intravenous use of DPH in a patient who died as well as the data obtained at postmortem examination and to discuss the possible causes of sudden death in the light of present knowledge concerning the mode of action of DPH

Case report

A [illegible]6-year-old female (M M) was admitted to Queens Hospital Center with a history of chest pain palpitations and shortness of breath She was transferred from a tuberculous ward where she had been followed for inactive tuberculosis

The patient noted the onset of angina several months prior to admission She was treated with digoxin 0 25 mg daily I N H 100 mg three times a day and Piridoxin 50 mg daily Physical examination revealed an elderly woman in respiratory distress Her blood pressure was 135/80 mm Hg and her pulse was 10[illegible] per minute and irregular The neck veins were markedly distended at 4[illegible] There were moist râles at both bases and rhonchi were scattered throughout both lung fields The apex beat was not palpable A Grade IV holosystolic murmur was present at the apex The liver was enlarged three fingerbreadths below the right costal margin Two-plus edema of the lower extremities was present The venous pressure was [illegible] mm of saline Chest x ray showed fibrotic changes in both lungs with pleural thickening and honeycombing in the left apex of the left lung The heart appeared enlarged in its transverse diameter

The ECG (Fig 1) showed regular sinus rhythm right ventricular hypertrophy and/or right bundle branch block with left anterior hemiblock (LAH) and many atrial and ventricular premature beats Digitalis was discontinued and oxygen was administered for relief of respiratory distress

Because of persistent runs of premature ventricular beats and the possibility that these were related to digitalis toxicity 100 mg of DPH was administered intravenously over a three minute period under continuous ECG monitoring DPH is considered to be very effective in the treatment of digitalis toxicity The rhythm strip (Fig 2 *A*) showed the presence of atrial and ventricular premature beats before DPH Three minutes after the onset of injection (*B*) the rhythm strip showed a regular nodal rhythm of [illegible] beats per minute then a half minute later the ventricular rate progressively slowed and asystole developed (*C*) The patient was externally paced (*D*) After half a minute the pacemaker failed and asystole again developed (*E*) All other attempts at resuscitation failed

Laboratory tests performed before treatment with DPH showed blood urea nitrogen (BUN) 13 mg per cent chloride 91 mEq per liter Na 134 mEq per liter and K 3 6 mEq per liter Analysis of arterial blood revealed a CO content of 33 mM per liter pH 7 47 P_{CO_2} 4[illegible] mm Hg P_{O_2} 43 mm Hg and oxygen saturation 80 per cent

At postmortem examination the heart weighed 5[illegible]0 grams and the myocardium was flabby The left atrium was 2 mm thick, the left ventricle was 15 mm thick and dilated with marked thickening of the papillary muscles and columnae carnae There was moderate calcification in the mitral valve ring The right ventricle was 8 mm thick and dilated The papillary muscles were flattened

The right atrium was 2 mm thick and dilated The coronary vessels were widely patent and no arteriosclerotic changes were seen There was no scarring or recent infarction in the myocardium Histologic examination of the myocardium revealed hypertrophy of the fibers and minimal focal hydropic changes The lungs showed diffusely thickened pleurae bronchi markedly dilated with a honeycomb appearance and large and small cavitations in the left lung which were lined by bronchial epithelium Severe emphysema as well as atelectasis were also present

Comments

In 1950 Harris and Kokernot[3] suggested DPH (dilantin) for the acute treatment of cardiac

From the Division of Cardiology Department of Medicine Queens Hospital Center The Long Island Jewish/Hillside Medical Center Clinical Campus of the State University of New York Medical School at Stony Brook

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Reprint requests to Dr Samuel Zoneraich Head, Division of Cardiology Queens Hospital Center 8[illegible]-68 164 St Jamaica, N Y 11[illegible]

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of ventricular conduction disturbances hypoxemia and metabolic abnormalities as precipitating factors are discussed

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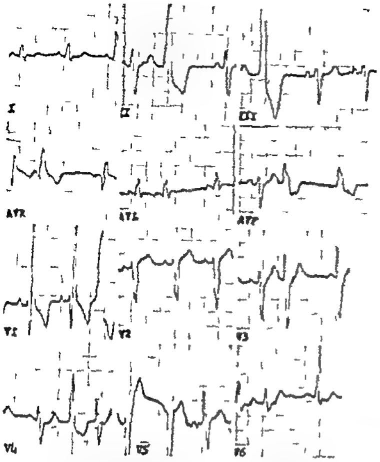

Fig 1 ECG showing sinus tachycardia rate 100 per minute right ventricular hypertrophy and/or right bundle branch block left anterior hemiblock and many APC's and PVC's

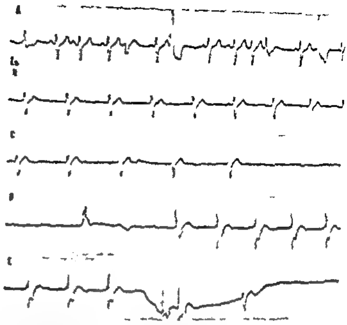

Fig 2 Rhythm strips (L_2) showing the sequence of ECG events following intravenous administration of 100 mg of DPH (see text)

arrhythmias They controlled ventricular tachycardia occurring after ligation of the anterior descending artery in dogs by using DPH in adequate amounts

Leonard was the first to use intravenous DPH in 1958 to convert a ventricular tachycardia complicating an acute myocardial infarction to regular sinus rhythm

The mechanisms underlying the antiarrhythmic effect of DPH have not been fully elucidated

The available data indicate that DPH reduces excitability and automaticity of the heart

Several deaths have been reported following intravenous dilantin administration The direct cause of these deaths has not yet been clarified

The deleterious effects of DPH are depression of myocardial contractility decreased peripheral vascular resistance[1] and disturbance of rate and rhythm[11] Recent reports[1,11] stress that in patients with heart disease and in normal man the atrioventricular (A V) nodal conduction is accelerated by therapeutic doses of intravenous DPH Larger doses of DPH used in animals produced a prolongation of the P R interval A V nodal block and cardiac arrest[11]

In all seven reported deaths the patients received only 150 to 250 mg of DPH doses which are usually recommended in the treatment of cardiac arrhythmias[14] Four of these patients developed nodal or idioventricular rhythm and then ventricular asystole The same ECG sequence was recorded in our patient The duration of the intravenous administration of DPH was three minutes in our case and two and a half minutes or less in four of the seven reported patients Six patients were receiving digitalis and four patients were considered to be digitoxic This patient had severe chronic lung disease with hypoxemia, metabolic disturbances and advanced intraventricular conduction disturbance (RBBB ± LAH) It is known that hypoxemia and alkalemia may produce serious arrhythmias[13] The sequence of events in this case suggest that in elderly patients with digitalis toxicity severe chronic lung disease producing hypoxia, and intraventricular conduction defects DPH used intravenously, even in usual dosages may be dangerous

Summary

A well documented (by ECG as well as autopsy) case of fatal ventricular asystole secondary to intravenous administration of sodium diphenylhydantoin is presented The possible role

hypertensive than in *normotensive* subjects[31] The former has been confirmed moreover whereas the latter is still disputed It is also well known clinically that the essential hypertensive subject responds to drugs affecting the sympathetic nervous system such as reserpine methyl dopa or guanethidine with a greater decrease in blood pressure than does the normotensive subject

What is the role if any of epinephrine (E) in the hypertensive process? A glance at the patterns of degradation makes it apparent that only normetanephrine and metanephrine are direct metabolites of NE and E 3 Methoxy 4 hydroxyphenylethylene glycol as well as vanillyl mandelic acid (VMA) are metabolites derived from both NE and E [3] In man moreover E as inferred from the relative proportion of urinary metanephrine and normetanephrine may comprise from 20 to 50 per cent of the total catecholamines produced in contrast to the much smaller proportion found in laboratory animals[3] Some of this however may result from N methylation of NE and its metabolites after release from sympathetic nerve endings[3] The effect of E on the circulation is different from that of NE of course[3] [3] In small doses it produces a net vasodilation with an increase in cardiac output and in blood pressure[3] but in large doses it produces a net vasoconstriction [3] [3] The action of E however varies from one vascular bed to another and the dose response curves with reference to vasodilation versus vasoconstriction may be quite different in the digits for example than in striated muscle or in the kidney[3] In the kidney the juxtaglomerular apparatus appears to be in part at least beta receptor activated[3] and the effect of E on the circulation may be modified by that of AT II

Some differences have appeared in essential hypertension when E and NE are considered separately rather than together One observer noted both hormones to be increased in the plasma in essential hypertension Only in established essential hypertension however was plasma NE found to be proportional to diastolic pressure In labile hypertension such a clear-cut proportion was not found Digital vascular reactivity to E has been found to be elevated from the normal particularly in labile hypertension but also in some patients with established hypertension The existence of both NE and E hyperreactivity in essential hypertension has been postulated and they may exist either separately or together With reference to E reactivity this is correlated with decreased retention of infused E as measured by the increased excretion of tritium in a 24 hour urine after a small intravenous dose of tritiated E (^{3}HE)[44] There is also significant correlation between E reactivity and emotional reaction to E infusion and probably to isoproterenol infusion as well E reactivity and E retention are also significantly correlated with percentage variation in both systolic and diastolic blood pressure[4] It has been demonstrated however that there is *no correlation* between E reactivity and characterologic anxiety although the hypertensive subject may respond to such anxiety by increasing his vasoconstriction with E infusion whereas the normotensive subject responds by increasing his cardiac output with such infusion [6] What is more E reactivity and retention correlate poorly, if at all with NE reactivity and retention[4] In addition it is well known that in general diurnal excretion of catecholamines is always greater than nocturnal excretion[47]

It must also be stated that plasma catecholamines can be elevated in conditions other than essential hypertension[13] [3] Pheochromocytoma has already been mentioned but such increases have also been observed in psychotic states although whether NE or E or both are elevated in such states is not clear[15] It is also well known to those studying catecholamine excretion for the purpose of identifying pheochromocytoma that very sick patients with fever or in coma will often have borderline concentrations impossible to distinguish from levels found in patients with pheochromocytoma [4]

In order to put some of these data together in a logical manner it is necessary in our opinion first to consider labile essential hypertension and established essential hypertension separately and also not to lump the catecholamines together but to consider E and NE separately These are two separate chemical substances each of which is secreted by the body in different ways and has different physiologic actions What makes this confusing moreover is that labile and established essential hypertension may exist separately or together

A major question that must be dealt with is how can the increased plasma disappearance rate of infused NE in essential hypertension be ex

The catecholamines in essential hypertension

Milton Mendlowitz, M D *
Nicolas D Vlachakis, M D
New York, N Y

How can the divergent data on catecholamine metabolism in essential hypertension be reconciled, if that is indeed possible Perhaps a logical explanation for some of the apparently conflicting data can be evolved without either dismissing certain observations as irrelevant or even incorrect, because of methodologic or observational defects

Let us first examine the data itself Most studies of the excretion of catecholamines and their metabolites of which several have been done in essential hypertension do not indicate much deviation from the normal [1-6] The fluctuation is often greater than in the normal group but the mean is the same In fact the differentiation of pheochromocytoma from essential hypertension depends on finding the urinary metabolites in the former instance above, and in the latter within the normal range [7]

Minor deviations with reference to specific urinary metabolites have been noticed [8] These deviations however, are small and frequently overlap with the normal values and are often not in accord with data accumulated by other investigators [9,10]

For methodologic reasons the question of whether norepinephrine (NE) turnover is normal or abnormal in essential hypertension had best be deferred It is clear, however that therapy with such drugs as reserpine methyldopa guanethidine or pargyline affects turnover profoundly in different ways [11,12]

From the Hypertension Division of the Department of Medicine Mount Sinai School of Medicine of the City University of New York New York
Received for publication July 27 1974
Reprint requests Dr Milton Mendlowitz Department of Medicine Mount Sinai School of Medicine Fifth Ave and 100 St New York N Y 10029
* The Joe Lowe and Louis Price Professor of Medicine

Earlier studies of plasma catecholamines[13,14] usually revealed normal values, but here methodologic difficulties might be at fault because newer methods including those using double isotope labels have revealed an increase in plasma catecholamines in essential hypertension in several different laboratories,[15-18] and no change from the normal in one laboratory [19] Also in one study, the plasma disappearance rate of infused labeled NE and its metabolites was more rapid in essential hypertensive than in normotensive subjects [20] On the other hand, plasma dopamine beta hydroxylase levels which are usually a measure of sympathetic nerve activity [1,21] have been found to range widely in normotensive as well as in essential hypertensive subjects [22] The uptake or retention of labeled NE (TNEE), on the other hand, has been found to be decreased when measured from the urinary excretion of the label [3] This phenomenon is however, very dose dependent, being apparent at low and disappearing at higher doses of labeled NE [23] In addition the "apparent NE secretion rate" (ANESR) which is measured by dividing the dose of tritium administered intravenously as ^{3}HNE by the specific activity of normetanephrine in a subsequently collected 24 hour urine is decreased in established essential hypertension, the decrease being due largely to increased excretion of tritium labeled normetanephrine [24] Vascular reactivity to infused NE [7] as well as to endogenous NE released by tyramine [8] is also increased in essential hypertension and the former is significantly correlated with the tritiated norepinephrine excretion (TNEE) and with the ANESR [7] Vascular reactivity to angiotensin II (AT II) however is also increased in essential hypertension [30] In addition, it has been demonstrated that stress increases the blood pressure and the excretion of catecholamines in the urine more in

hydroxylase release in accordance with the theory of exocytosis [31]

In established essential hypertension the increase in NE reactivity is due largely to the decreased ability of the neural stores to take up released NE making more available to the receptors and to the plasma The evidence for this is the decrease in retention of intravenous ^{3}HNE in established essential hypertension [5] and the proportion between plasma NE and diastolic blood pressure [9] Whether this effect is associated with structural changes in the heart and blood vessels or is affected by electrolyte changes in the interstitial fluid [5] or is a primary abnormality in sympathetic nerve proteins is of course still conjectural

It does seem clear however that the features characteristic of labile hypertension and established hypertension may either co exist or be present separately It is not clear on the other hand which labile type progresses to become established and if this occurs what the mechanisms are for such an evolution

Summary

The evidence for involvement of the catecholamines and their metabolites in essential hypertension is presented Labile and established essential hypertension should be considered individually in this respect although they may exist separately or together Labile essential hypertension is more related to increased secretion as well as increased response to and decreased retention of epinephrine rather than norepinephrine whereas established essential hypertension is more related to similar aspects of norepinephrine release and metabolism Whether pure epinephrine hyperresponsiveness abnormal metabolism and secretion evolves into the pure norepinephrine hyperresponsiveness and abnormal metabolism of uncomplicated established essential hypertension can only be proved by long term longitudinal study Such investigation would also be required to identify the evolution of mixed types of the disease

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plained The answer here is probably methodologic When turnover is measured from specific activity of urinary VMA, E as well as NE is incorporated in the calculations Also, steady state conditions which are necessary for the measurement of turnover do not occur until a variable time interval, depending upon the dose, has elapsed after infusion of the label Measurements before such a state is achieved are probably in error One might conclude therefore that the more rapid plasma disappearance of NE and its metabolites after infusion of ³HNE in essential hypertension probably does reflect an increase in turnover although this remains to be proved specifically [45] It may merely be another manifestation of decreased retention

Another discrepancy that requires reconciliation is the fact that many observers find on the average that the urinary excretion of the catecholamines and their metabolites in essential hypertension is no greater than normal [1, 16, 45] Also plasma dopamine beta hydroxylase levels are found to be either normal, low or elevated in essential hypertensive subjects [24] although one group of workers find it to be proportional to diastolic pressure in established essential hypertension [46] This enzyme is often a measure of sympathetic nervous activity [1, 2, 21] On the other hand plasma catecholamines and particularly plasma NE is elevated in some patients with essential hypertension [3, 17]

Again here, methodologic factors are at fault Many urinary assays of catecholamine metabolites are done on early morning specimens per milligram of creatinine This is good for the differentiation of essential hypertension from pheochromocytoma but it may miss the circadian daylight upswing of the catecholamines in the hypertensive subject as against the normal subject [47] or the increased excretion with psychic effort [48] admittedly still disputed In fact if the catecholamine store is low in essential hypertension and neural uptake and re uptake impaired the circadian fluctuation in plasma catecholamine might be exaggerated with low values at night and high values during the day Also, E must always be differentiated from NE in such studies and labile clearly separated from established essential hypertension It appears that psychic effort increases E excretion [49] whereas the upright position increases NE excretion and plasma renin activity (PRA) [50] Also usually one metabolite, or E or NE alone, is studied but unless the hormones and all their metabolites are measured together in a 24 hour urine, the estimate of catecholamine output from urinary excretion will be faulty

It must also be remembered that retention of NE is decreased in established essential hypertension [35] and that retention of E is decreased in labile essential hypertension [41] and these conditions may exist separately or together This implies that the NE released from nerve endings and the E from chromaffin tissue in essential hypertension is distributed differently than normal, more going to receptors and into the plasma and less back into the neural store or to other binding sites In the long run, however this would require replenishment of the stores by increased synthesis It is understandable therefore that dopamine beta hydroxylase might be quite variable under these conditions and this is compounded by the fact that there appears to be a soluble and membrane bound form of this enzyme [1, 51, 52] It is unclear whether the enzyme, like NE is also subject to re uptake Under these conditions, moreover increased neural firing would produce much more of an effect in the essential hypertensive subject than in the normal subject and this is consistent with observations in the clinic In the hypertensive subjects moreover, there might be phasic swings which are greater than in the normotensive subject Thus the decreased re uptake might be compensated for to some extent, by decreased release of NE with normal neural firing whereas with increased firing even if the release is normal for a given stimulus the decreased re uptake would make for an increased effect

Let us now present what appears to be the role of the catecholamines in essential hypertension according to the state of the art at the present time Labile hypertension is related more to E metabolism than to NE metabolism [41] It is probably associated with an increase in secretion of epinephrine most apparent during stress [31, 49] There is also an increase in sensitivity of beta adrenergic receptors to such secretion probably because of a decrease in nonreceptor binding of the hormone NE release is also increased in labile hypertension,[16] but this is probably more of a consequence of sympathetic neural firing stimulated by the increase in E secretion Such increased NE release, if it occurred, would be associated with increased dopamine beta

hydroxylase release in accordance with the theory of exocytosis[23]

In established essential hypertension the increase in NE reactivity is due largely to the decreased ability of the neural stores to take up released NE making more available to the receptors and to the plasma The evidence for this is the decrease in retention of intravenous ³HNE in established essential hypertension[5] and the proportion between plasma NE and diastolic blood pressure Whether this effect is associated with structural changes in the heart and blood vessels[5] or is affected by electrolyte changes in the interstitial fluid[25] or is a primary abnormality in sympathetic nerve proteins is of course still conjectural

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Fundamentals of clinical cardiology

Systolic sounds

John F Stapleton M D
W Proctor Harvey M D
Washington D C

For many years clinicians have detected extra heart sounds during systole Early descriptions and pathogenetic speculation can be found in the writings of such French clinicians as Cuffer and Barbillion Potain[1] Petit[2] Gallivardin Lian and Welti and others

Since their earliest descriptions extra sounds in systole have been regarded as benign findings In 1913 Gallivardin described pleuropericardial adhesions in three autopsied patients who had systolic sounds during life Until the past decade many systolic sounds were attributed to such extracardiac causes The advent of angiocardiography and intracardiac phonocardiography have now clarified the genesis of most of these sounds revealing underlying cardiac structural changes which were previously unsuspected

For descriptive purposes systolic sounds can be divided into three main categories semilunar ejection sounds systolic clicks and miscellaneous systolic sounds

Since systolic sounds of all three categories usually have crisp high pitched character the term click is often applied To avoid confusion we limit this term to the systolic clicks caused by mitral leaflet prolapse designating as sounds all other systolic vibrations too brief to be called murmurs Since systolic clicks usually occur in the middle of systole the expression midsystolic click often applies

From the Department of Medicine Division of Cardiology Georgetown University Hospital, Washington D C

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Reprint requests John F Stapleton M D Department of Medicine Georgetown University Hospital, 3800 Reservoir Rd., N W Washington, D C 20007

Ejection sounds

Ejection sounds are brief sounds occurring as the name implies at the onset of systolic flow into the great arteries The sounds are usually high pitched and frequently occur close enough to the first sound to simulate splitting of the first sound Since ejection sounds are often loudest over the cardiac base they may be mistaken for first heart sounds in individuals whose first heart sounds are faint in the pulmonic and aortic areas This error is easily made when the ejection sound is low pitched like the usual first sound

Ejection sounds are classified as pulmonic ejection sounds relating to right ventricular ejection or as aortic ejection sounds relating to left ventricular ejection (Fig 1)

Pulmonic ejection sounds Pulmonic ejection sounds are best heard in the pulmonic area and along the mid and lower left sternal edge The sound often diminishes with inspiration sometimes disappearing completely becoming more audible during expiration Inspiratory loss of sound especially characterizes the ejection sound of valvular pulmonic stenosis (Fig 2)

Since inspiration increases flow through the right heart and generally augments right heart murmurs inspiratory reduction of pulmonic ejection sounds seems paradoxical Simultaneous recordings of heart sounds with right ventricular and pulmonary artery pressure pulses have indicated that ejection sounds occur when right ventricular systolic pressure exceeds pulmonary artery pressure thereby initiating systolic ejection Precisely timed cineangiographic frames reveal ejection sounds to coincide with the abrupt arrest of pulmonic valve cusps (or congenital diaphragm) when maximally protruded into the pulmonary artery, the sound immediately precedes the flow of contrast media into the

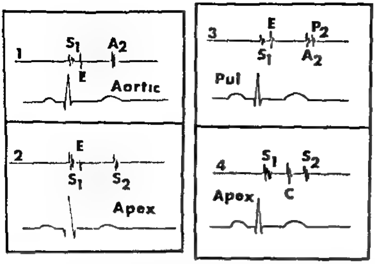

Fig 1 Composite schematic representation of ejection sounds and midsystolic click *Panel 1* displays aortic ejection sound in aortic area Note brevity of sound and loudness relative to the first sound in this location *Panel 2* displays aortic ejection sound as heard at the apex The first sound is now louder than the ejection sound *Panel 3* displays a pulmonic ejection sound at the pulmonic area This sound is brief but may be louder than the first sound in this area as indicated in this drawing The sound is frequently localized to this region and diminishes or disappears during expiration *Panel 4* displays a midsystolic click at the apex This sound is brief high pitched and may vary its location in systole S first heart sound *F* ejection sound *A* aortic closure sound S second heart sound *P* pulmonic closure sound *C* systolic click

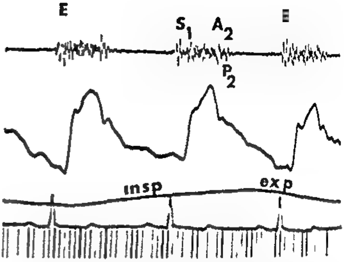

Fig 2 Pulmonic stenosis of moderate severity in young adult right ventricular systolic peak pressure 80 Pulmonic ejection click (*F*) close to first heart sound (*S*) Note inspiratory subsidence of click *A* aortic closure sound *P* pulmonic closure sound *insp* inspiration *exp* expiration (From Stapleton JF Am Fam Physician 9 79 1974)

pulmonary artery[7] Inspiration, by increasing right ventricular diastolic volume causes preliminary bulging of the pulmonic valve into the pulmonary artery Early systolic protrusion is thereby lessened with resultant diminution or loss of the associated sound Expiration by reducing right ventricular diastolic volume permits a more slack pulmonic valve position ventricular contraction will then cause greater valve excursion and sound

A pulmonic ejection sound is usually present in valvular pulmonic stenosis but not in infundibular stenosis The average interval between the first heart sound and ejection sound in pulmonic stenosis is 0 04 second but varies with severity moving closer to the first sound as stenosis becomes more severe The sound is most consistently present in mild pulmonic stenosis as a rule, the more severe the stenosis the less likely an ejection sound Advanced pulmonic stenosis may exist without any ejection sound when pulmonary artery diastolic pressure is very low right ventricular systolic pressure may open the pulmonic valve during the first heart sound obscuring any ejection sound Rarely, atrial systole may elevate right ventricular end diastolic pressure to levels exceeding pulmonary artery diastolic pressure When such presystolic pressure crossover occurs an ejection sound may appear with the timing of an atrial or 4th heart sound

Pulmonary ejection sounds immediately precede pulmonary ejection murmurs, when present Rare exceptions have been recorded of ejection murmurs beginning before the ejection sound These cases plus the later timing of ejection sounds which occur with pulmonary hypertension have suggested a vascular genesis for some of the ejection sounds which accompany pulmonary hypertension Hyperkinetic arterial distention is well known to cause 'pistol shot or impact sounds That sudden tautness of the pulmonary artery might cause early systolic sound is suggested by a recent case report, which describes an early systolic sound apparently pulmonic, in the absence of pulmonic valve cusps[10] Ejection sounds become more frequent as pulmonary artery pressure rises being common in primary pulmonary hypertension and in pulmonary hypertension due to ventricular septal defect, atrial septal defect, or patent ductus arteriosus (Fig 3)[8,11] The pulmonic ejection sounds of advanced pulmonary hypertension may or may not diminish upon inspiration as do other pulmonic ejection sounds Possibly high pulmonic diastolic pressure and reduced right ventricular distensibility lessen the effect of inspiration upon pulmonic valve position

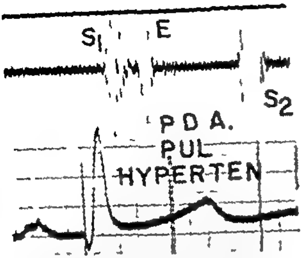

Fig 3 Pulmonic ejection sound (E) of severe pulmonary hypertension due to patent ductus arteriosus. This sound occurs later than the ejection sound of pulmonic stenosis 0 08 sec after S_1 in this case S_1 First heart sound S_2, second heart sound E ejection sound.

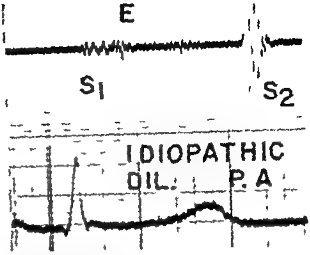

Fig 4 Pulmonic ejection click of idiopathic dilatation of pulmonary artery S_1 First heart sound E ejection sound S_2 second heart sound.

Pulmonic ejection sounds regularly accompany idiopathic dilatation of the pulmonary artery with or without respiratory variation (Fig 4) Occasionally heard in atrial septal defect they are rare in ventricular septal defect unless complicated by pulmonary hypertension[8] When a moderate pulmonic systolic murmur and widened splitting of the second sound coexist mild pulmonic stenosis or atrial septal defect may be present In such instances a prominent pulmonic ejection sound diminishing or disappearing with inspiration strongly favors pulmonic stenosis over atrial septal defect

Pulmonic ejection sounds also occur with the Taussig Bing complex with pulmonic incompetence with transposition of the great arteries and occasionally with Fallot s tetralogy Pulmonary hypertensive mitral stenosis may cause a pulmonic ejection sound which is masked by the delayed sound of late mitral valve closure

Occasionally an individual presents a pulmonic ejection sound without other evidence of disease Sometimes it is not possible to establish the mechanism of such sounds Perhaps these persons have a minor anomaly of pulmonic valve structure Further follow up may elucidate such cases.

Aortic ejection sounds High pitched early systolic sounds can often be heard at the aortic area in patients with abnormalities of the aortic valve and ascending aorta. These are aortic ejection sounds analogous to the pulmonic sounds just discussed

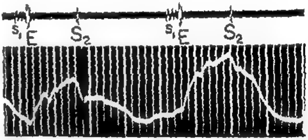

Fig 5A Aortic ejection sound (E) of an asymptomatic 40-year-old housewife with mild aortic stenosis Note that sound coincides with onset of carotid upstroke Curve recorded at the apex. S_1 First heart sound S_2 second heart sound

Cineangiographic correlations between these ejection sounds and aortic valve motion in valvular aortic stenosis indicate that this sound occurs as the aortic valve achieves its maximum systolic protrusion (or domes) into the aorta preceding actual ejection by about 0 015 second Usually best heard in the aortic area this sound is often clearly audible at the apex and sometimes best heard there Elderly and emphysematous patients may present aortic ejection sounds at the apex which are poorly heard at the base but may transmit to the upper sternum and right sternoclavicular joint Unlike pulmonic ejection sounds

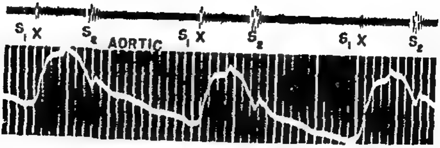

Fig 5B Aortic ejection sound (X) of an asymptomatic patient with aortic coarctation occurring 0 08 sec after onset of first heart sound Curve recorded in the aortic area S_1 First heart sound S_2 second heart sound

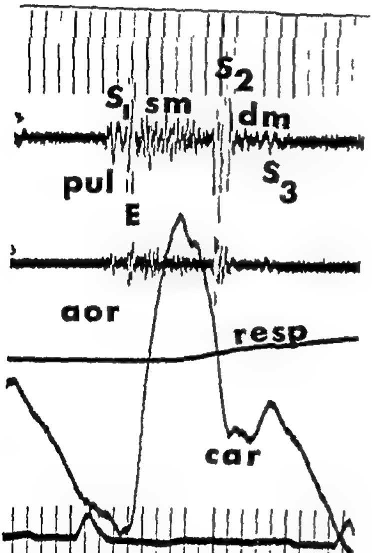

Fig ■ Prominent aortic ejection sound (*E*) transmitting widely in young man with severe aortic regurgitation *S* First heart sound *S* second heart sound *S* third heart sound *dm* diastolic murmur *aor* aortic area *pul* pulmonic area *car* carotid pulse *resp* respiration

aortic ejection sounds are usually unaffected by respiration, inspiration occasionally diminishes sound intensity, perhaps by transiently reducing left ventricular stroke volume or by imposing more air filled lung over the source of sound These sounds are usually heard readily When the first sound and ejection sound are both prominent, *the sequence resembles—and may be* mistaken for—an atrial or fourth heart sound and first sound This erroneous interpretation is most likely when the ejection sound is well heard at the apex *Usually the high pitched and brief char*acter of the ejection sound permits its differentiation from the lower pitched more prolonged first heart sound The distinction may be difficult when the *ejection sound is lower pitched* than usual

Aortic ejection sounds are commonly associated with aortic stenosis (Fig 5,*A*) ' '' Congenital valvular aortic stenosis regularly causes ejection sounds Supravalvular and subvalvular stenosis do not Acquired valvular stenosis may *also cause ejection sounds but often does not* Whether or not an ejection sound accompanies valvular stenosis seems to depend upon valve mobility Patients with calcific aortic stenosis and *frozen valves do not have ejection* sounds and have diminished or absent aortic second sounds Acquired stenosis which has diminished but not eliminated valve mobility may cause faint ejection sounds and diminished aortic second sounds Acquired stenosis which has not impaired valve mobility at all may present a prominent ejection *sound and normal aortic second sound*

Hypertrophic subaortic stenosis rarely causes ejection sounds Low pitched early systolic sounds have been heard which could represent abrupt beginning of murmur vibrations caused by sudden obstructive narrowing of the left ventricular outflow tract during early systole '

Aortic ejection sounds frequently are heard in patients with aortic coarctation (Fig 5 *B*) usually with an aortic systolic murmur Aortic regurgitation *may be present in such cases, but occa*sionally no obvious aortic valve dysfunction exists These patients probably have congenital bicuspid aortic valves *long survival following*

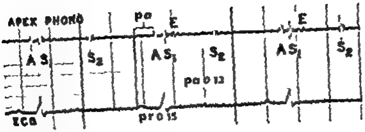

Fig 7 Aortic ejection click (*E*) in severe hypertension Prominent atrial sound (*A*) also present *S* First heart sound *S* second heart sound

resection of coarcted aorta may permit the evolution of aortic stenosis in some of these patients as has been reported

Severe tetralogy of Fallot can cause aortic ejection sounds These patients may have prominent ascending aortas resulting from biventricular ejection into the aorta The more severe the obstruction to right ventricular outflow the more likely an aortic ejection sound Patients with pseudotruncus arteriosus usually have aortic ejection sounds These sounds may differ from other aortic ejection sounds in that inspiration may reduce sound intensity This unusual response of an aortic event to respiration probably relates in some way to the partial right ventricular origin of aortic flow

Systolic ejection sounds also commonly accompany truncus arteriosus An early systolic sound is frequently present with severe aortic regurgitation This sound sometimes occurs as late as 0 10 second after the first heart sound later than other aortic ejection sounds The hyperdynamic systolic aortic expansion of aortic regurgitation suggests that this late sound could derive from sudden tautness of the distended aortic wall abrupt deceleration of valve cusps may account for those aortic ejection sounds of aortic regurgitation which occur when ejection begins (Fig 6) Occasionally an ejection sound accompanies systemic hypertension (Fig 7) It is not clear whether these sounds represent exaggerated aortic valve opening or arise from the hyperkinetic aortic wall as do some early systolic sounds of aortic regurgitation

Systolic sounds commonly accompany patent ductus arteriosus are often multiple and may occupy various parts of systole Pulmonic ejection sounds are frequent and relate to the hyperdynamic dilated pulmonary artery due either to a large flow as in normotensive patent ductus or to high pressure as in pulmonary hypertensive patent ductus Since high left ventricular output with aortic dilatation can result from patent ductus aortic ejection sounds may also appear Occasionally aortic and pulmonic ejection sounds coexist when this is the case, the pulmonic sound precedes the aortic sound A recent report describes two separate pulmonic ejection sounds in the same patient the first coinciding with beginning right ventricular ejection and the second coinciding with the arrival of the aortic systolic pressure peak at the ductal orifice [4]

Multiple discrete systolic sounds may also occur at various times in systole and diastole in large ductal shunts featuring noisy turbulent flow with loud continuous murmurs These sounds called eddy sounds are loudest in the pulmonic area and occupy predominantly late systole and early diastole The sounds may change timing from cycle to cycle Rare patients with patent ductus arteriosus may have pulmonic and aortic ejection sounds eddy sounds and a continuous murmur [15]

A further variety of ejection sounds are those produced by prosthetic aortic valves The ball or disc causes a brief sound upon opening this sound is often called an opening click because of the high pitch which derives from prosthetic material It occurs slightly later (about 0 07 second after S_1) than the ejection sound of the natural valve this delay is explained by the time required for the ball or disc to move against the retaining cage or struts Usually the prosthetic opening click is single sometimes several clicks occur occasionally recurring throughout systole

Careful serial auscultation of the prosthetic aortic opening click can disclose developing ball variance [16] Most prosthetic devices produce an opening click as loud or nearly as loud as the closing click in early diastole Softening of the opening click especially when the pitch of the sound changes to a lower frequency strongly

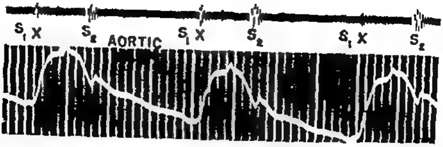

Fig 5B Aortic ejection sound (X) of an asymptomatic patient with aortic coarctation occurring 0 08 sec after onset of first heart sound Curve recorded in the aortic area S First heart sound S_2 second heart sound

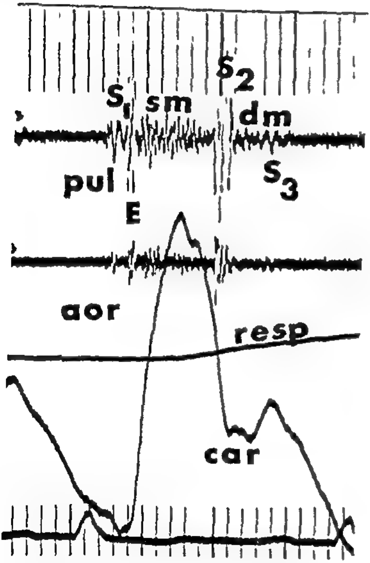

Fig 6 Prominent aortic ejection sound (E) transmitting widely in young man with severe aortic regurgitation S First heart sound S_2 second heart sound S third heart sound *dm* diastolic murmur *aor* aortic area *pul* pulmonic area *car* carotid pulse *resp* respiration

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Hypertrophic subaortic stenosis rarely causes ejection sounds Low pitched early systolic sounds have been heard which could represent abrupt beginning of murmur vibrations caused by sudden obstructive narrowing of the left ventricular outflow tract during early systole[1]

Aortic ejection sounds frequently are heard in patients with aortic coarctation (Fig 5 *B*) usually with an aortic systolic murmur Aortic regurgitation may be present in such cases but occasionally no obvious aortic valve dysfunction exists These patients probably have congenital bicuspid aortic valves long survival following

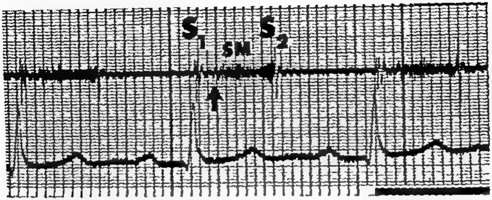

Fig 10 Systolic click (arrow) of mitral leaflet prolapse initiates systolic murmur of mitral regurgitation Cardiac catheterization revealed mild mitral stenosis and regurgitation suggesting rheumatic etiology Systole is clear prior to click. S_1 First heart sound S_2 second heart sound SM systolic murmur

Multiple clicks close together create a grating or scratching sound resembling the friction rub of pericarditis Some patients have been referred with this diagnosis

It does not require special auscultatory skill to hear systolic clicks they are well within the range of ordinary hearing However they are sometimes overlooked when the examiner does not focus his specific attention on high pitched sounds in systole

Events such as inspiration standing inhaling amyl nitrate or the Valsalva maneuver which reduce left ventricular volume may increase chordal slack causing earlier leaflet prolapse, these circumstances will move the click and murmur onset closer to the first sound Reduced left ventricular volume may also transiently produce a late systolic murmur or may convert a late systolic murmur into a more prolonged and occasionally holosystolic one Conversely events such as squatting or bradycardia which increase left volume may reduce chordal slack delay the systolic click and shorten or eliminate the murmur

The murmur associated with the systolic click is usually Grade III or less but sometimes louder and though commonly late systolic occasionally begins in early systole (Fig 10) The click usually precedes the murmur uncommonly murmur vibrations may begin before the click Sometimes the late systolic murmur exists without a systolic click or the click may accompany the murmur intermittently (Fig 8 *C*) Occasionally the late systolic murmurs which accompany systolic clicks are curiously raucous (Fig 8 *D*) Called systolic whoops or honks these sonorous

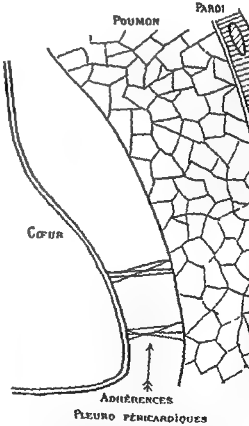

Fig 11 Sketch of pleuropericardial adhesions found at autopsy in case of Gallavardin with systolic click during life (From Gallavardin, L. Lyon Med 121 409 1913)

murmurs are often intermittent and may be induced by standing or by exercise[20,21] This murmur may occur only upon expiration and may also be induced by inotropic drugs At times it is so loud as to be heard with unaided ear sometimes a few feet away

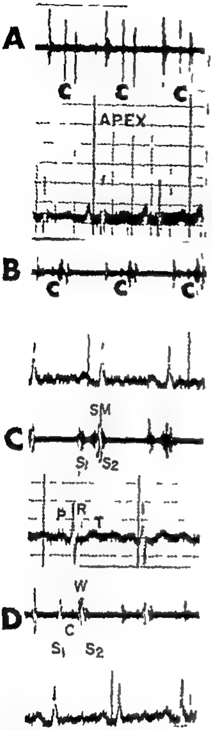

Fig 8 A Midsystolic click (C) without associated murmur B Midsystolic click (C) followed by late systolic murmur C Late systolic murmur (SM) without systolic click D Midsystolic click (C) followed by musical late systolic murmur or whoop (W) S First heart sound S_2 second heart sound

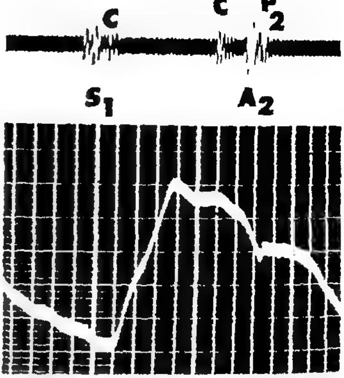

Fig 9 Early and late systolic sounds in 17 year old female patient without clinical heart disease The late sound occurs 0 07 sec before the second heart sound—a time interval similar to that between the second heart sound and a mitral opening snap Sounds in late systole have led to the erroneous diagnosis of mitral stenosis S_1 First heart sound C systolic sound A_2 aortic closure sound P_2 pulmonic closure sound

suggests ball variance or clots on the prosthetic valve Disappearance of the opening click requires prompt investigation and, often, valve replacement The combination of echocardiography phonocardiography, and cineangiography has greatly aided evaluation of prosthetic valve function

Timing of the prosthetic aortic opening click may relate to left ventricular contractility so that delayed or late closure resulting from slow ball or disc movement could indicate reduced contractility whereas the early closure of rapid ball or disc movement could indicate enhanced contractility [17]

Systolic clicks

Clicks occurring later than semilunar valve opening have been recognized for many years Such clicks are usually midsystolic, hence the descriptive designation as "midsystolic clicks" or "nonejection clicks" (Fig 8 A) Since these clicks often initiate a late systolic murmur the term "midsystolic click-late systolic murmur syndrome" is also used (Fig 8, B) Other anatomic labels are sometimes employed as will be discussed

The clicks are usually best heard at the apex generally transmitting well to the left parasternal region While usually midsystolic, the clicks may occur in early or late systole [18, 19] Occasionally a click is sufficiently early to simulate an ejection sound or sufficiently late to simulate a second sound-mitral opening snap sequence (Fig 9)

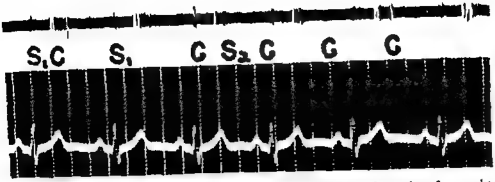

Fig 13 Peculiar crunching sounds (*C*) of varying timing in both systole and diastole resulting from mediastinal emphysema in otherwise healthy ?6-year-old man *S* First heart sound *S* second heart sound

found in relatives who have no evidence of any systemic disorders

Miscellaneous

Occasional systolic sounds are neither ejection sounds nor prolapsed leaflet clicks but represent other uncommon structural defects

Ventricular aneurysms have long been known to cause systolic sounds [4, 5, 32, 33] Usually midsystolic this sound is occasionally early systolic coinciding with outward systolic aneurysmal movement and has been attributed either to abrupt tautness of the aneurysm or to aneurysmal impingement upon the internal chest wall Since papillary muscle disease often coexists with ventricular aneurysm systolic clicks associated with ventricular aneurysm could arise from the mitral leaflet prolapse which may occur when a diseased papillary muscle fails to maintain adequate chordal tension during systole

Aneurysms of the membranous interventricular septum are frequently associated with small ventricular septal defects Over 90 per cent of these patients have an early systolic high pitched clicking sound occurring during the ascending limb of the carotid artery pressure pulse slightly later than ejection sounds The sounds are localized to the lower left parasternal region do not radiate and are best heard during expiration This phenomenon is sometimes referred to as the windsock effect Pulmonic ejection sounds are rarely found in ventricular septal defect with normal pulmonary artery pressure When the patient with a ventricular septal defect and normal pulmonary artery pressure presents an early systolic sound aneurysm of the membranous septum should be suspected Emergence of a systolic sound not previously present could mean diminution of the septal aperture although none of 54 recently reported patients with membranous septal aneurysms closed their defects during 4 years of observation [35]

A recent case report describes a systolic sound associated with pericardial effusion [36] The timing of this sound varied from midsystole to late systole it became loud during inspiration faint during expiration and disappeared after surgical drainage and anterior pericardiectomy

Ebstein s anomaly frequently exaggerates and delays tricuspid closure causing a loud snapping sound which can simulate an ejection sound Although this sound often resembles an early systolic extra sound it is actually a delayed and intensified component of the first heart sound

Congestive cardiomyopathy may cause late systolic clicks as described in a recent report of two cases [37] One patient also had a late systolic murmur and the other an intermittent systolic whoop or honk Both patients had mitral regurgitation but neither had prolapsing leaflets on angiocardiography and one mitral valve appeared normal at surgery The mechanism is not clear in these cases but malposition and/or malfunction of a papillary muscle could account for late tensing of chordae tendinae or of a mitral leaflet Several patients reported to have systolic clicks due to ischemic papillary muscle disease presented clicks in late systole just before the second heart sound [38] Another possible mechanism might relate to the dilated mitral annulus requiring annuloplasty in one of the patients with cardiomyopathy since there is evidence to suggest that a dilated mitral annulus can cause systolic clicks

Pneumothorax may cause unusual systolic sounds as may mediastinal emphysema (Fig 13)

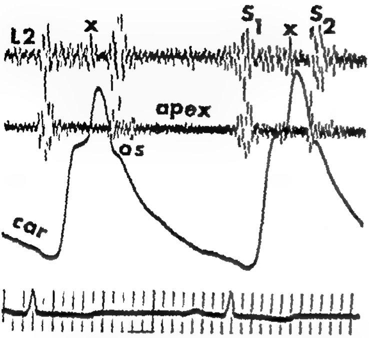

Fig 12 A 46-year-old man with mitral stenosis and regurgitation and aortic regurgitation and severe pulmonary hypertension Note systolic click (X) in latter half of systole This click was loudest at left upper sternal edge Pathogenesis uncertain S_1 first heart sound S_2 second heart sound OS mitral opening snap car carotid pulse

The auscultatory phenomena just described usually occur in patients enjoying apparently good cardiac health For many years systolic clicks were regarded as benign findings, most likely of extracardiac origin This belief was fortified by the historical report of Gallivardin in 1913 which described pleuropericardial adhesions in three autopsied patients who had had systolic clicks during life (Fig 11)[4] While adhesions can cause clicking sounds synchronous with respiratory or cardiac motion, many angiographic and intracardiac phonocardiographic studies in the past decade have disclosed intrinsic cardiac abnormalities in patients with systolic clicks[1 3] The most common of these consists of abrupt protrusion of a bulging mitral leaflet into the left atrium during systole Usually the posterior leaflet is involved the anterior or both leaflets can be so affected The bulge or prolapse generally begins at the time of the click and at the onset of the murmur A jet of contrast material often enters the left atrium from the left ventricle in late systole in these cases confirming the presence of mild late systolic mitral regurgitation and explaining the late systolic murmur These angiographic findings have led some observers to label this entity as the billowing or prolapsing' leaflet syndrome

Other angiographic studies have revealed various aberrations of the left ventricular contraction pattern leading some authors to conclude that many patients with the systolic click-late systolic murmur syndrome have an underlying cardiomyopathy with secondary prolapse of mitral leaflets[18]

Whatever the mechanism of mitral leaflet prolapse, the click probably arises from abrupt tensing of chordae tendineae or of the prolapsed leaflet itself The syndrome has many causes Most commonly no etiology is apparent, abnormally elongated chordae and/or myxomatous leaflet change are generally blamed in such instances This syndrome is frequent in Marfan s syndrome, at least some idiopathic cases are considered to represent formes frustes of Marfan s syndrome because similar valve histology has been found in the few valves so examined[5] The idiopathic systolic click syndrome is sufficiently benign and its morphologic documentation sufficiently recent that few cases have come to autopsy or surgery Longer follow up should clarify the significance of these findings

Various other heart diseases have been associated with systolic clicks[1 3] Papillary muscle disease either from primary cardiomyopathy or from myocardial infarction may lead to systolic clicks[1 4] Failure of a papillary muscle and/or the adjacent left ventricular wall to contract may allow its chordae tendineae to become slack during systole with resultant leaflet prolapse Other causes of systolic clicks include mitral valve surgery trauma rheumatic valve disease (Figs 10 12) and bacterial endocarditis Systolic clicks which occur after mitral commissurotomy are often low pitched early systolic may be multiple and may be loud[1]

An interesting clinical association links systolic clicks with ostium secundum atrial septal defect[8] Features of the septal defect are typical although in some, normal splitting of the second heart sound is heard instead of the wide fixed splitting which usually characterizes the second sound of atrial septal defect The curious normalization of the second sound of atrial septal defect in those cases is unexplained

The systolic click has now been amply confirmed to be familial in some instances[9 10] Occasionally features of Marfan s syndrome accompany familial clicks and murmurs more often the clicks and/or late systolic murmurs are

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In both conditions (which may coexist) crackling or crunching sounds may result from cardiac movement against air-containing tissue; such sounds will then occur rhythmically with each heart beat. Frequently, additional clicking sounds result from respiratory movement which obscure those due to cardiac movement, but occasionally the sounds are limited to cardiac systole. Changes of posture will often bring out additional sounds in such individuals.

The advent of pacemaker therapy of cardiac conduction disturbances has created a new category of heart sounds, namely, those caused by pacemakers. These sounds may occur at any time during the cardiac cycle, are frequently of brief clicking quality but may also be low pitched. These sounds are best heard at the apex or lower left sternal border and may be loud or faint. When pacemaker sounds occur in patients in sinus rhythm whose pacing has continued at an independent rate, a confusing sequence of sounds may result. Since pacemaker sounds may occur even when the pacing stimulus occurs during the absolute refractory period, an extracardiac genesis is likely. Intercostal muscle contraction may cause pacemaker sounds; usually such sounds are presystolic, but occasionally systolic sounds occur. The pacing catheter itself can produce a discrete systolic sound or a musical murmur varying from low to high frequency. Removing or repositioning the catheter may eliminate the sound or murmur.

Conclusions

Extra heart sounds commonly occur during systole. Such sounds usually indicate underlying structural abnormality of the heart. There are two major categories: ejection sounds arising from a semilunar valve or great artery and midsystolic clicks arising from prolapsing mitral valve leaflets. Pulmonic and aortic ejection sounds are high pitched sounds in early systole immediately following the first heart sound. Pulmonic ejection sounds are loudest over the pulmonary area, whereas aortic ejection sounds are loudest over the aortic region, often transmitting well to the apex.

Most patients with congenital aortic or pulmonic stenosis have ejection sounds occurring at the onset of ejection, coinciding with maximal outward bulge of the stenotic cusps or diaphragm.

Pulmonic ejection sounds are frequently heard in patients with pulmonary hypertension and dilatation of the main pulmonary artery; these sounds also regularly accompany idiopathic dilatation of the pulmonary artery but are less commonly heard in patients with uncomplicated atrial or ventricular septal defects. Aortic ejection sounds frequently occur in aortic coarctation, probably denoting underlying bicuspid aortic valves. Such sounds are also heard in patients with aortic regurgitation, truncus arteriosus, tetralogy of Fallot, and aortic valvular prostheses.

Systolic clicks commonly occur with late systolic murmurs at the apex. Usually these clicks and murmurs are found in otherwise healthy individuals; angiocardiographic studies generally reveal midsystolic prolapse of one or both mitral leaflets into the left atrium, often accompanied by late systolic regurgitation. The syndrome is found with Marfan's syndrome, papillary muscle disease of ischemic or other cause, and following trauma or mitral commissurotomy.

Ventricular aneurysms rarely may cause early or midsystolic clicks. Aneurysms of the membranous interventricular septum regularly cause early systolic sounds. Pericardial effusion, hypertrophic cardiomyopathy, pneumothorax, mediastinal emphysema, and pacemakers may also cause systolic sounds.

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Lysosomal mechanisms in production of tissue damage during myocardial ischemia and the effects of treatment with steroids

Arthur C Fox M D
Sylvia Hoffstein Ph D
Gerald Weissmann M D
New York N Y

Mortality from acute myocardial infarction has been decreased by prompt detection and treatment of arrhythmias and it is now important to evaluate interventions which might decrease damage to the acutely ischemic or jeopardized myocardium In general these include hemodynamic interventions which improve myocardial blood flow or decrease metabolic demands, and biochemical interventions which augment anerobic metabolism facilitate the flux of substrates and metabolites or decrease early structural damage (Table I) We have investigated the last category By a combined ultrastructural and biochemical study using an experimental model of myocardial infarction we have demonstrated a correlation between lysosomal disruption and early cell damage with possible amelioration by early treatment with pharmacologic doses of methylprednisolone

The rapid biochemical functional and structural changes which occur in the heart during early ischemia (Table II) have been well described[1,2] but the links between metabolic changes and structural damage have not been established In other tissues ischemia and its consequent intracellular acidosis have been shown to disrupt lysosomes Lysosomal hydrolases (proteases lipases glycosidases) are then no longer membrane bound and are released into the cytoplasm where they have the potential to initiate or augment the digestion of structural components Earlier studies showed the presence in heart muscle of lysosomal enzymes capable of producing the morphologic changes seen in early ischemia[3,4] during ischemia, intracellular pH falls towards levels known to disrupt lysosomes and to favor hydrolytic activity[5,6] Several studies showed that lysosomal enzymes from ischemic hearts shift from the membrane bound sedimentable fraction to the free, non sedimentable fraction However it was questionable whether lysosomal mechanisms in heart were important in the pathogenesis of ischemic injury since many of the fractionation studies were inadequate since lysosomal activity may have come from non myocardial cells and since morphologic studies showed only a few conventional lysosomes and these changed little after infarction

We examined myocardial biopsies from normal dog hearts with the electron microscope both for general morphology and for cytochemical distribution of the lysosomal marker enzymes acid phosphatase and aryl sulfatase[6] Lysosomes of 'conventional' appearance were sparse and far fewer than those seen in other tissues However membrane bound reaction products of the two enzyme markers were found throughout the cell and were particularly concentrated within the elements of the sarcoplasmic reticulum (S R), where they highlighted the round and elongated profiles of the longitudinal components and lateral sacs at the diads triads and cell periphery Human myocardium obtained during surgery showed similar evidence of lysosomal enzyme activity in the S R (Fig 1)

From the Department of Medicine New York University School of Medicine New York N Y

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Reprint requests to Arthur C Fox M D Dept of Medicine New York University School of Medicine 550 First Ave New York N Y 10016

Table I Possible approaches to reduction of infarct size

I *Hemodynamic*
- A. Increase O delivery
  - 1 Augment diastolic perfusion (pressors intra aortic balloon)
  - 2 Oxygen therapy
  - 3 Reperfusion via bypass surgery
- B. Decrease oxygen needs (MVO)
  - Decrease RATE (analgesics antiarrhythmics propranolol)
  - PRELOAD (digitalis in CHF nitrites nitroprusside)
  - AFTERLOAD (nitrites nitroprusside trimethapan intraaortic balloon)
  - INOTROPY (propranolol verapamil?)

II *Biochemical*
- A. Augment anerobic metabolism
  - Glucose potassium insulin Hypertonic glucose Decrease H (alkali) Krebs cycle intermediates
- B. Augment diffusion of substrates and metabolites
  - Hyaluronidase Hyperosmolar solutions (decrease cell swelling)
- C. Decrease metabolically mediated cell damage
  - Decrease H (alkali) Protect cellular and subcellular membranes (steroids) inhibit released lysosomal hydrolases

Table II Sequence of events during early myocardial ischemia

1 to 60 seconds

Early biochemical changes
1. Decrease in oxidative phosphorylation
2. Glycogenolysis
3. Shift to anerobic glycolysis
4. Accumulation of lactate and H
5. Inactivation of membrane Na K ATPase pumps → K egress and changes in electrical repolarization
6. Inhibition of excitation/contraction couplin (H binding to Ca sites on troponin loss of sarcolemmal sarcotubular and mitochondrial regulation of Ca)

Hemodynamic changes

Secondary to loss of regional contraction effects of poor regional contraction on global function of heart initiation of rhythm disturbances

5 to 30 minutes

Later biochemical changes early and reversible morphologic changes

Severe falls in CrP ATP cessation of glycolysis as H accumulates intracellular accumulation of Na and H O → cell swelling and changes in capillary endothelium → no reflow phenomenon

30 to 60 minutes

Initiation of irreversible damage to cell membranes to mitochondria and other organelles such as lysosomes

We then produced myocardial infarctions in open-chest dogs by ligating the left anterior descending artery and in closed chest dogs by electrical induction of coronary thrombosis Cytochemical evidence of lysosomal activity in the S R began to decrease as early as one hour after infarction and this correlated well with progressive damage to the mitochondria and myofibrils. Severely damaged areas at the center of infarctions showed more loss of enzyme activity than better preserved marginal areas Tissue fractionation studies showed that in normal subendocardial areas over 50 per cent of the activity of the lysosomal marker enzymes acid phosphatase and β glucuronidase was in the membrane-bound fraction After two hours of ischemia there was a significant redistribution to the unbound or free fraction in the subendocardium a region which is at greater hemodynamic jeopardy This early redistribution of lysosomal activity with a subsequent fall and a later rise in total activity as heterologous cells entered the damaged area correlated well with cytochemical and morphologic changes.

In concomitant studies colloidal lanthanum was used as a probe for early impairment of cell membrane integrity during ischemia[3] Lanthanum is an electron dense marker normally limited to the extracellular space It began to penetrate the cytoplasm after only one hour of ischemia Although lanthanum was excluded from some minimally injured cells it was present within all severely damaged cells

These results suggested that in marginally ischemic zones and perhaps in the center of infarcts cell injury might occur by at least two mechanisms in one an early loss of sarcolemmal integrity leads to uncontrolled entry of ions and macromolecules and loss of soluble cytoplasmic constituents In another there is early intracellular release of substances perhaps from lysosomes which initiate intracellular damage The two processes may well be interrelated but a lack of synchrony between them could account for some of the morphologic heterogeneity seen in early ischemic lesions with normal and damaged cells juxtaposed

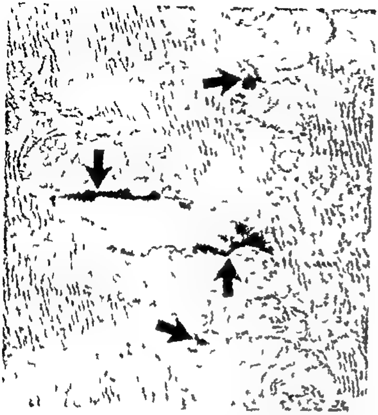

Fig 1 Portion of a myocardial cell from human left ventricular wall incubated to localize acid phosphatase activity Reaction product (arrows) is localized within elements of the sarcoplasmic reticulum Magnification × 25 000

Since early ischemia seemed to impair function of cellular and subcellular membranes we next examined the effects of corticosteroids, which stabilize a wide variety of natural and synthetic biomembranes Steroids are presumably delivered to ischemic areas by collateral flow and have been shown to penetrate myocardial cells during hemorrhagic shock At one half hour after coronary occlusion we gave eight dogs 50 mg per kilogram of body weight of methylprednisolone which did not by itself produce significant hemodynamic effects These dogs were paired with control animals not treated after coronary occlusion Biopsies were taken from infarcted and normal areas of each heart at two hours after occlusion and compared Infarcted subendocardial areas in treated animals showed significantly less redistribution of lysosomal enzymes into the supernatant fraction than there was in infarcts from untreated animals This biochemical evidence for improved lysosomal stability correlated well with cytochemical evidence for preservation of lyosomal markers in the sarcoplasmic reticulum and with better ultrastructural integrity of mitochondria[11]

Our studies in animals therefore clearly showed that lysosomes are among the subcellular organelles injured early in ischemia, that their potentially damaging hydrolases are released at this time, and that steroids may inhibit the process The lysosomal mechanism may not be a primary event in cell injury, but a secondary result of diffuse damage to cell membranes just as the protection by steroids might reflect non specific preservation of all cell membranes Other studies in animals have shown a similar protective effect of pharmacologic doses of steroids on lysosomal redistribution in cats at five hours after infarction and a decrease in infarct size in cats at five hours and in dogs at 24 hours

In man the effects of treatment with steroids during myocardial infarction are far less clear Early studies were limited by poor controls wide variation in dosages and the absence of accurate in vivo methods for estimating infarct size There have been appropriate warnings that prolonged use of steroids might even impair healing and lead to formation of aneurysms

With the development of an ingenious mathematical model for use in estimating and predicting infarct size by serial measurement of serum CPK levels it was hoped that the effects of therapeutic interventions might be more definitively studied in vivo In animal studies estimated infarct sizes correlated well with pathologic findings in man mortality rates were higher after infarctions of larger size However there has been recent criticism of the validity of using the CPK method to study the effects of therapeutic interventions on the ultimate size of evolving infarctions Although estimates of developed infarct size from computed CPK curves may be useful for comparing groups of patients predictions of infarct size in individuals by extrapolation from the rate of CPK release in the first five to six hours requires further validation We confirmed the qualitative usefulness of the method for estimating developed infarct size in man by measuring CPK release over 24 hour periods In a series of 40 patients 24 anterior infarctions were significantly larger than 16 inferior infarctions (89 ± 10 vs 54 ± 8 CPK gram equivalents $p = 0.001$) 6 of the 8 deaths in the group occurred among the 11 patients with infarctions estimated to be over 100 CPK gram equivalents

Two studies of the effects of corticosteroid therapy on infarct size in man have yielded

disparate results Morrison and colleagues' reported that completed infarcts were 20 per cent smaller than predicted size in 42 patients treated with pharmacologic doses of methylprednisolone within the first 24 hours over all mortality rates after six months were decreased However de Mello and associates[19] who gave comparable doses more frequently over 48 hours reported adverse effects completed infarcts exceeded predicted size by 72 per cent and there were prolonged elevations in serum levels of the MB isoenzyme of CPK

These conflicting results make it clear that there is at present no basis for routine treatment of patients with corticosteroids in an attempt to decrease infarct size despite the encouraging results of animal studies The use of corticosteroids in patients should be limited to carefully controlled experimental groups in which infarct size is measured by methods of proved reliability We feel that steroids may ultimately be shown to help preserve cell structure during early myocardial ischemia until other protective mechanisms such as better regional perfusion can be invoked Clinical application may be limited to single large doses immediately after the onset of ischemia perhaps in combination with other approaches listed in Table I We agree with Braunwald and Maroko[20] that as with all methods proposed to limit infarct size the use of corticosteroids must be carefully tested before clinical application can be recommended

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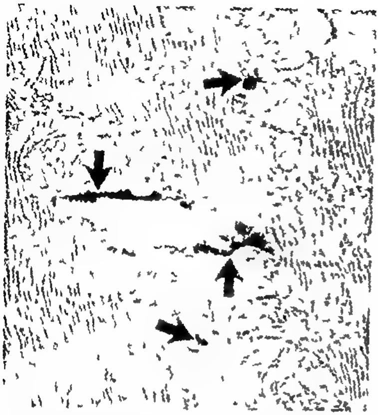

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I thank the following colleagues for supplying material Drs P J Richardson Kings College Hospital London D Harmjanz formerly of the Medizinische Hochschule Hannover West Germany C M Oakley and T Peters Royal Postgraduate Medical School London W Jesse University of Wurzburg Germany and my colleagues at the National Heart Hospital, London

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Estimation of left ventricular volumes using a simplified method

Measurement of left ventricular volume is now an established procedure in the assessment of left ventricular function and is of increasing importance in the clinical hemodynamics laboratory Traditional methods for calculating left ventricular volume are tedious and time consuming. The area length method is commonly employed to derive the minor axis from the relation $D = 4A/\pi L$, where D = minor axis A = the area and L = the long axis of an ellipsoid The ventricle is assumed to be an ellipsoid of revolution and the following equation yields volume

$$V = \pi/6 \cdot D_p^2 \cdot L_p \cdot (CF) \qquad (1)$$

where CF is a factor to correct for magnification and p is a subscript referring to projected measurements.

In order to arrive at volume the following steps are taken The end-diastolic and end-systolic frames of the ventriculogram are projected onto paper where the diastolic and systolic ventricular outlines are drawn in pencil. The area of each contour is measured by means of an integrating planimeter The correction factor is calculated by superimposing the projection of a 1 cm grid over the left ventricular shape in mid-cycle The actual area A (subscript a refers to actual values) of the ventricle is obtained by counting the number of squares enclosed by the ventricular outline The projected area A_p of this mid-cycle frame is obtained by planimetry The ratio A_a/A_p in mid-cycle yields (CF) the area correction factor The projected long axis L_p is obtained directly from the ventricular outline in both end-diastolic and end-systolic frames

The purpose of this paper is to report a simplified method for estimating left ventricular volume a method which requires no drawing can be carried out directly on the projector and obviates planimetry of the ventricular outlines.

Left ventriculograms of 28 children were obtained following direct opacification of the left ventricle or pulmonary angiography The cineangiograms were exposed on 16 mm cine film at 120 frames per second in the anteroposterior projection The optimal cardiac cycle was chosen avoiding extrasystolic and postextrasystolic beats. The end-diastolic and end systolic frames were examined with the projection of the calibration grid superimposed The distance between the x ray tube and the center of the left ventricle (assumed to be at mid chest) was determined for each patient A set of grids was filmed at different distances from the image intensifier and maintained as standards for the measurement of actual areas and correction factors. The projected areas of the end diastolic and end-systolic frames were determined by counting the number of squares within the respective ventricular contours. The longest length was directly measured from the left margin of the aortic valve to the apex A mid-cycle frame was superimposed on the projected image of the grid filmed at the estimated distance of the center of the left ventricle from the image intensifier A direct linear correction factor (LCF) was obtained by measuring a linear dimension of the superimposed projected grid and expressing this as a ratio of its known true dimension.

$$LCF = LD_p/LD_a \qquad (2)$$

where LD_p = the projected linear dimension and LD_a = the

Annotations

Diagnostic value of the endomyocardial bioptome

Since the early 1960's an instrument, the bioptome (Konno's bioptome), making use of conventional techniques of cardiac catheterization, has been employed to obtain fresh endomyocardial tissue. As a method of investigation it is now becoming more widely used throughout the world and has superceded to a large extent past methods which have included needle biopsy and elective thoracotomy. Surgical operation where removal of myocardium formed an essential part of the operation also permitted examination of fresh endomyocardial tissue in some cases.

The original instrument was adapted to an ordinary intracardiac catheter. A bioptome modified from the Olympus fiberoptic bronchoscope biopsy forceps (BF 5B2) has recently been developed at King's College Hospital. Konno's bioptome was employed by the Japanese workers who obtained biopsies from approximately 500 cases and concentrated on classification of myocardial disease. The potential value permitting a more detailed clinical diagnosis was also emphasized, but it would appear that the clinical diagnosis was only in doubt in a few cases.

In my opinion the undertaking of such a procedure should be limited to those patients for whom conventional methods of cardiologic investigation have failed to establish a diagnosis and in whom direct visualization of endomyocardial tissue can reasonably be expected to yield a helpful result.

Such a study, using either the original bioptome or the King's College Hospital modification, has recently been reported, concentrating on the useful diagnostic results which may be derived from such a procedure. Biopsy material was pooled from five centers. It was analyzed from 67 patients, 49 of whom were suspected of suffering from a form of cardiomyopathy, the term being limited to those conditions which were of unknown cause and not associated with disease elsewhere in the body. The clinical classification was used. Three specimens each measuring approximately 3 mm in diameter were usually taken from each patient. With the exception of three cases, the material was obtained from the right ventricle. More accurate positioning of the instrument in the ventricular chamber was facilitated by fluoroscopy and intracardiac electrocardiography. Tissue was examined histologically in every instance and, wherever possible, histochemically, electron microscopically, and cytochemically. The results showed that a definite pathologic diagnosis helpful to the clinician was possible in 65 per cent of patients. The material from the remaining patients was either classified as "unhelpful" or as "failure." The former applied when only equivocal diagnostic criteria were found, for example, in cases of hypertrophic cardiomyopathy where indices previously described were well below 50 per cent. Classification under "failure" included absence of the diagnostic element, such as endomyocardial fibrosis where no endocardium could be identified.

The writer's experience has now increased to the examination of material from 112 patients, and the results have remained virtually identical to those obtained from the smaller series of cases.

Another aspect of the diagnostic value of transvenous biopsies has been reported on a group of patients following cardiac transplantations. A percutaneous approach through the right internal jugular vein was used employing a specially designed instrument. From animal studies it had been learned that clinical manifestations of acute episodes of rejection are preceded by histologic changes by up to 48 hours. Similar findings were obtained in human cases, and out of a total of 37 acute cardiac allograft rejections, 35 have been successfully reversed. The new approach to the problem of acute rejection has led to improved management with encouraging results of the survival of patients.

The question arises whether or not the small pieces of endomyocardial tissue obtained by using the bioptome or its modified versions is representative of the underlying cardiac disease process. In cases of transplanted hearts this would certainly appear to be so. As to subsequent diagnostic confirmation in other patients, corroborative evidence has been obtained from a few cases who have subsequently died—not as a result of the bioptome procedure—or from a small number of patients who, as the result of the biopsy investigation, underwent surgery.

The results reported so far indicate that this method of investigation can be of particular diagnostic value when every other means of establishing a clinical diagnosis has failed. It is likely that more helpful results will be obtained when the suspected disease process is widespread (such as in acute rejection, myocarditis, or congestive cardiomyopathy) or when the suspected abnormality can be located accurately (such as intracardiac tumor or hypertrophic cardiomyopathy). In those cases where scattered lesions are suspected, for example, sarcoidosis or rheumatic myocarditis, less frequent useful information can be expected, even if right and left ventricular biopsies are undertaken.

The technique is safe but carries the usual risks of cardiac catheterization. Reported complications have included atrial fibrillation, nodal rhythm, and severe ventricular tachycardia. Other complications have included right-sided pneumothoraces, donor atrial flutter, and premature ventricular contraction.

Provided that the indications are clear, this method is invaluable in establishing a diagnosis of cardiac disease.

The application of these techniques does not end with establishing a diagnosis. The ease with which fresh endomyocardial tissue can now be obtained permits biochemical analysis and viral studies. Investigations along these lines will hopefully shed some light on the etiology or etiologies of cardiomyopathy.

E. G. J. Olsen
National Heart Hospital
London, England

In terms of hypovolemia I believe that many anesthetists do not put up enough intravenous infusions (to cover para operative normal water requirements as well as blood) and do not give enough fluid when the infusion is up (How many of your patients are thirsty after operation?) In some centers every patient has an intravenous drip put up before anesthesia begins. Somewhere between the two extremes probably is more satisfactory

We must all have seen patients for operation at midday who have had nothing to drink since late the previous evening and who then on the operating table have to contend with further reduction in blood volume from bleeding and sweating Surely a cup of tea and biscuit given not less than four hours before premedication does no harm and can only help to stimulate blood flow?

Looking further afield could it be that the published results following treatment for prevention of deep-vein thrombosis following cardiac infarction vary due to varying degrees of hydration?

Are cases of venous thrombosis following strokes due to a fear of giving old people too much fluid?

Do well controlled long term unconscious patients in intensive-care units seem to show a relatively low incidence of leg deep-vein thrombosis because the central venous pressure is maintained more near normal?

From other anesthetic aspects the prolonged recovery from anesthesia with its accompanying immobilization and hypoventilation and recognized associated dangers may produce a tranquil time for the patient, but is often due to an unnecessary overdose" of anesthesia, or to incorrect timing in the giving of analgesics

In an operation where the patient is paralyzed and asleep the anesthetist must largely concentrate on the likelihood of awareness and on the prevention of undue pain postoperatively Of course we want the patient preoperatively tranquil and postoperatively pain free but too much is too much

The likelihood of awareness, I believe should be gauged on a mental estimation of the preoperative metabolic rate rather than body weight per se I have previously shown that the alteration in arterial Pa_{CO} following the same premedication (in Jamaica) shows an inverse linear relationship to metabolic rate as expressed as a percentage of normal. Thus a thinner lighter nervous individual may require more premedication and/or sleep agent than a fatter heavier but more tranquil one

This approach is supported by Claridge

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Thus I believe that the modern anesthetist must think more broadly in terms of preserving a normal central venous pressure Coupled with this he must ensure that the preoperative patient is adequately sedated but not oversedated (remember the accumulative night sedation effect) that during the operation adrenergic activity in the normal patient should not be unduly suppressed and that postoperatively the patient should be quickly awake (after five minutes in recovery following a relaxant technique) with good muscle tone and with postoperative pain tending to be treated by titration in the recovery room rather than blindly on the operating table

These things, the avoidance of polypharmacy blindly given and our physiotherapists, should be the greatest factors to concentrate on in the fight against deep-vein thrombosis

J Michael Simpson M B B.S F.F.A R C.S
St Nicolaas Ziekenhuis
Waalwijk The Netherlands

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Of smoking and the respiratory tract

The publicity and propaganda that smoking produces carcinoma of the lungs and heart disease have diverted the attention of all people from the more important fact that even though these claims are true the incidences of these illnesses are relatively minor when it is realized that all (100 per cent) of the people who smoke have chronic diseases of their entire respiratory tract All smokers have chronic pharyngitis chronic paranasal sinusitis, chronic laryngitis chronic tracheitis, chronic bronchitis and bronchiectasis and many are destined to have serious emphysema Furthermore acute respiratory tract infections are prone to develop upon these chronic diseases. Any physician who remembers or reviews the

Table I Correlation coefficients and regression equations

End systolic volume index	r = 0 986	SFE = ±1 33	Y = 0 9569 X + 0 697
End diastolic volume index	r = 0 981	SFE = ± 3 35	Y = 0 9112 X + 3 57
Stroke volume index	r = 0 988	SEF = ± 2 39	Y = 0 9159 X + 2.57
Ejection fraction	r = 0 980	SFE = ± 0 02	Y = 0 9290 X + 5 21

Table II

	Proposed method		*Dodge Kasser and Kennedy*	
	Mean	*S D*	*Mean*	*S D*
End diastolic volume (Ml /M)	21 2	± 8	21	± 8
End systolic volume (Ml /M)	70 6	± 17	70 4	± 16
Stroke volume (Ml /M²)	49 6	± 16	49 4	± 15
Ejection Fraction	0 68	± 0 11	0 66	± 0 15

actual linear dimension The relation between this LCF and the CF utilized in the standard procedure is as follows

$$LCF = \sqrt{A\ /A} = 1/CF \qquad (3)$$

Equation I can be rewritten as

$$V = 0\ 84 \bullet A\ /L_y \bullet LCF \qquad (4)$$

The results obtained by the two methods were analyzed and compared statistically (Tables I and II) Our simplified method gave results which correlated well with the more cumbersome classical methods The proposed method eliminates the need for planimetry, a desk calculator and pencil drawings of the projected outlines and it is hoped that it may prove useful and time saving in the routine cardiac catheterization laboratory

Eduardo Meaney
Jacques St Pierre
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Department of Pediatrics
Hôpital Ste-Justine
Montréal Québec Canada
and Department of Medicine
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Prevention of deep-vein thrombosis

The large volume of literature published over the last two years on the subject of deep vein thrombosis serves to illustrate how great is the just concern of the thinking medical world over this very worrying and potentially dangerous condition but the etiologic diversities of the condition necessitate fundamental thinking in considering priorities for prevention of its occurrence

Thus in the paraoperative period just how important is the actual surgery performed in general terms on the incidence of deep-vein thrombosis? Is it the trauma of the knife or the stretching of tissues that one must consider? Does a rough operator produce higher figures than a gentler one? If it is tissue trauma what is the relative incidence of deep vein thrombosis in nonoperable trauma cases in intensive care units?

While not forgetting the much valuable contributory research work on the fibrinolytic system and even the evidence that cases developing deep vein thrombosis may be anticipated before surgery I believe that the occurrence figures throughout the world as detected by the ¹²⁵I fibrinogen method vary too widely for the operation itself again in general terms to be of great importance

As I have suggested elsewhere I believe the degree of blood flow in the deep veins of the leg to be the most important etiologic factor and that the avoidance of hypovolemia is the primary consideration in the prevention of the thrombotic condition

Many anesthetists must begin to think in broader horizons for their patients and even be prepared to modify their "standard" techniques considerably It is easy to speak of position on the operating table removal of skeletal muscle tone sweating, direct pelvic surgical trauma paraoperative vomiting postoperative hypoventilation and prolonged immobilization as being all of direct and vital importance but it is the thinking standard of the anesthetist that is of paramount importance

The normal human body can resist the sometime insults imposed on it by poor quality anesthesia the end result being the same However one insult it cannot cope with is prolonged paraoperative reduction in deep vein blood flow in the legs

In terms of hypovolemia I believe that many anesthetists do not put up enough intravenous infusions (to cover para operative normal" water requirements as well as blood) and do not give enough fluid when the infusion is up (How many of your patients are thirsty after operation?) In some centers every patient has an intravenous drip put up before anesthesia begins. Somewhere between the two extremes probably is more satisfactory

We must all have seen patients for operation at midday who have had nothing to drink since late the previous evening and who then on the operating table have to contend with further reduction in blood volume from bleeding and sweating Surely a cup of tea and biscuit given not less than four hours before premedication does no harm and can only help to stimulate blood flow?

Looking further afield could it be that the published results following treatment for prevention of deep vein thrombosis following cardiac infarction vary due to varying degrees of hydration?

Are cases of venous thrombosis following strokes due to a fear of giving old people too much fluid?

Do well controlled long term unconscious patients in intensive-care units seem to show a relatively low incidence of leg deep-vein thrombosis because the central venous pressure is maintained more near normal?

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St Nicolaas Ziekenhuis
Waalwijk The Netherlands

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Stroke volume index	r = 0.988	S.E.E. = ± 2.39	Y = 0.9459 X + 2.57
Ejection fraction	r = 0.980	S.E.E. = ± 0.02	Y = 0.9290 X + 5.21

Table II

	Proposed method		Dodge Kasser and Kennedy	
	Mean	S.D	Mean	S.D
End-diastolic volume (ML/M)	21.2	± 8	21	± 8
End systolic volume (Ml /M²)	70.6	± 17	70.4	± 16
Stroke volume (Ml /M²)	49.6	± 16	49.4	± 15
Ejection Fraction	0.68	± 0.11	0.66	± 0.15

actual linear dimension The relation between this LCF and the CF utilized in the standard procedure is as follows

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Equation 1 can be rewritten as

$$V = 0.84 \bullet A^{2}/L_{2} \bullet \mathrm{LCF} \quad (4)$$

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Letters to the Editor

Importance of the lead strength in ST changes produced by exercise

To the Editor

There is concern over the lack of sensitivity and specificity of the exercise electrocardiogram in detecting coronary disease. Efforts to improve the correlation have included varying S-T criteria, the S-T index of McHenry and associates and the S-T integral of Sheffield and co-workers. The focus of these evaluations has been entirely upon the S-T segment. However, in reviewing our exercise tests it became evident that the voltage of the leads was related to the amount of S-T depression.

We recorded the bipolar (V) monitoring lead with the unipolar chest leads during the postexercise period. The bipolar lead has the negative electrode placed below the right clavicle and the positive electrode at the usual V chest position. Sequential records were obtained of V, V, V, and the V at the immediate, two, four and six minute interval postexercise. Thirty-seven tests had an S-T depression in one of these leads of at least 0.1 mV with the S-T segment being horizontal or downsloping. The two minute reading was selected for the following measurements because of baseline stability. The R wave height was recorded and the S-T depression to the nearest 0.05 mV was recorded for the four leads. An S-T depression to R wave height ratio was also calculated for each of the leads. The mean results for these tests are given in the table below.

Table I

	V	V	V	V
R height mV	1.2	1.4	1.0	2.0
S-T depression	0.64	0.[illegible]	0.36	1.28
S-T/R	0.0[illegible]	0.05	0.36	0.06

It is evident that the S-T depression is related to the R wave height. In addition, the S-T depression to R wave height ratio was nearly identical for V, V and V.

The importance of lead strength has been alluded to by Blackburn and colleagues[6] in the early work on the bipolar chest leads. The Scandinavian Committee on ECG Classification also took note of this by recommending a 25 per cent increase in S-T depression over the usual Minnesota Code to read the test as abnormal when using the bipolar lead system. It would seem essential that more attention be given to lead strength in the future evaluations of the exercise electrocardiogram.

John T. Santinga, M.D.
Heart Station
The University of Michigan Medical Center
University Hospital
Ann Arbor, Mich. 48104

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Transchest electrical ventricular defibrillation

To the Editor

Techniques and equipment for transchest electrical ventricular defibrillation are changing and those who apply this procedure must be aware of these changes. It has recently been reported that defibrillation with damped sinusoidal waveforms requires a minimum dose of electricity based on patient body weight. The defibrillators presently available cannot deliver a dose that is adequate to defibrillate consistently the ventricles of most patients who weigh 80 kilograms or more.

Defibrillation is accomplished by passing an electric current of adequate density and appropriate waveform through the heart. One way to increase current density is to increase the electrical output of defibrillators; such high-output equipment (maximum output 500 to 1000 watt/seconds of delivered energy) will probably be available in the near future. Because the output of these units will greatly exceed the energy required for defibrillation of small patients, users must carefully select the appropriate electrical dose since overdosage damages the myocardium. Responsible medical practice will no longer be to use automatically the maximum output in an attempt to defibrillate the ventricles.

Another way to increase current density is to decrease the

histology of the mucous membranes and epithelial lining realizes the extreme delicacy of these tissues. Irritation by tobacco smoke predisposes to necrosis or at least to some injury to those tissues. This damage in turn results in infection, inflammatory reactions, purulent discharges, post-nasal drip, cough, etc.—all symptoms and signs of respiratory tract disease. The many sorts of medical therapy employed to control the infections and injury further tend to damage the tissues and may even result in serious drug reaction. If the patient would only stop smoking, the results, though slow, would be rewarding. But, most important of all, people should not even begin to smoke.

Cancer and heart disease are important, but their incidence among smokers is minor compared to the fact that *all* smokers (millions of people) have chronic diseases of their entire respiratory tract. Furthermore, the dentures and teeth of most smokers are dirty and stained and their breath is unpleasant.[1]

C. E. Burch, MD
Tulane University School of Medicine and Charity Hospital
New Orleans, La.

spells, in our opinion. Whereas in the normal ventilation is controlled with negative feedback (decreasing CO and increasing O with increasing ventilation) this is not the case in cyanotic congenital heart disease with diminished pulmonary blood flow

I will not repeat the evidence for paroxysmal hyperpnea except that positive inotropic effects would be totally incapable of explaining these blue spells in patients with pulmonary atresia which account for 70 per cent of these spells Paroxysmal hyperpnea although not a primary event in tachyrhythmias could nevertheless operate as a central mechanism that would maintain the spells once begun Steeg and Hordof have clearly proven that tachyrhythmia can initiate the spells and this contribution is extremely valuable

Warren G Guntheroth M.D
Professor of Pediatrics
Head Division of Pediatric Cardiology
School of Medicine
Department of Pediatrics
University of Washington
Seattle Wash 98105

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Reply

To the Editor

We appreciate Dr Guntheroth s remarks Technically we agree with Dr Guntheroth s definition of spasm and concur that increased right ventricular outflow tract obstruction" would have been a better term It should be stated that the use of spasm in this regard appears to be rather protean Indeed, Dr Guntheroth employs it without modification in his discussion of the subject.

We did not mean to imply that paroxysmal hyperpnea was the sole etiology according to Guntheroth and we have no reason to doubt his explanation for spells, one widely accepted in pediatric cardiologic circles. Dr Guntheroth does state however that "hyperpnea is the crucial event in these spells tending, we believe to detract from initiating episodes such as a tachyarrhythmia.

Our patient showed no clinical or laboratory evidence of either hyperventilation or hyperpnea at any time during the cardiovascular procedure which, perhaps, may be explained by the premedication

Carl N Steeg M.D
Associate Professor Clinical Pediatrics
Director Pediatric Cardiovascular Laboratory
Allan J Hordof M.D
Assistant Professor Pediatrics
Department of Pediatrics
College of Physicians & Surgeons
Columbia University
630 W 168th St
New York N Y 10032

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Sudden death in sexual activity

To the Editor

Dr Green has discussed sudden death during coitus in his excellent article which was titled Sexual activity and the postmyocardial infarction patient According to him this subject was not so clear and he stated that some factors such as emotion a big meal or alcohol can be causative factors in unexpected death.

We have studied the electrocardiographic changes during sexual intercourse by utilizing a Holter monitor In cases with old myocardial infarction or coronary insufficiency ST segment depression with marked tachycardia was observed although these patients did not suffer from any precordial pain or discomfort However the same patients suffered from precordial pain during exercise when their electrocardiograms showed less ST segment depression and a lesser degree of tachycardia We believe that this phenomen is related to the "analgesic effect" of sexual activity (Fig 1)

We would like to state that this "analgesic effect may play

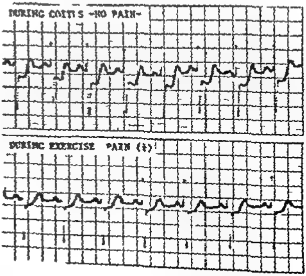

Fig 1

transthoracic impedance which can be done by increasing the surface area of the electrode paddles or by using electrode paste with a low resistivity Larger paddles (12 8 cm diameter) not only lower transthoracic impedance but they also produce less myocardial damage than do smaller paddles when the same amount of energy is applied [3]

A few commercially available defibrillators use a trapezoidal waveform This waveform also requires adequate current density based on body weight but the energy doses required for defibrillation with these waveforms are not the same as the doses with damped sinusoidal waveforms The efficacy of trapezoidal units on human patients has not been reported but we know that the trapezoidal units now available like the sinusoidal units available cannot defibrillate most animal subjects who weigh over 80 kilograms

All patients can be defibrillated with the appropriate dose of energy even heavy patients who require more energy than do light patients and patients who have had an acute myocardial infarction a condition known to raise the dose required Therefore satisfactory defibrillation technique requires that equipment with adequate output be available and that the users follow the proper procedure so that even the heavy patient with an acute myocardial infarction can be defibrillated

Gordon A Ewy M D
Arizona Medical Center
University of Arizona
Tucson Arizona 85724
W A Tacker Jr M D Ph D
Purdue University
West Lafayette Indiana 47907

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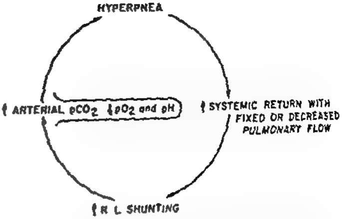

Fig 1 The regenerative cycle involved in paroxysmal hyperpnea in tetralogy of Fallot Note the paradox of a lowered arterial saturation with hyperpnea in contrast to the effect of hyperpnea in the normal

Increased cyanosis in VSD with outflow tract obstruction

To the Editor

In the August issue of the AMERICAN HEART JOURNAL Steeg and Hordof[1] documented for the first time the production of increased cyanosis in a tetrad of Fallot due to reduced pulmonary blood flow without reduced systemic blood flow A previous report by King and Franch[2] in 1971 reported well documented instances of increased obstruction to the outflow tract of the right ventricle with tachyrhythmias but they did not have data on the systemic vascular resistance According ly Steeg and Hordof have made a conclusive case for increasing obstruction of the outflow tract as a cause for increasing cyanosis The authors acknowledge two possible mechanisms of increasing obstruction that could be ascribed to tachycardia One method would be inherent in inadequate filling of the right ventricle which would necessarily reduce the cross sectional area of the outflow tract and increase the obstruction to flow The other mechanism is referred to by Steeg and Hordof by the term originally applied by Paul Wood spasm of the right ventricular outflow tract It is unfortunate that Wood used this term and that it continues to be used by cardiologists Spasm is alien to myocardial physiology Tetanus is a characteristic feature of skeletal and smooth muscle but occurs in the myocardium only under unphysiological states such as extreme derangements of calcium concentration and combinations of hypothermia and rapid pacing Increasing heart rate does have a positive inotropic effect and a case can be made for this method of increasing the obstruction of the right ventricle but this is a well accepted event with real physiological basis as opposed to the concept of spasm

The authors quoted my chapter on Tetralogy of Fallot in an incomplete fashion and implied that I suggested paroxysmal hyperpnea as the sole cause of spells in Fallot s tetrad The original work appeared in 1965 and the key figure is in Fig 1 It is clear that decreased pulmonary flow is accepted as a method of increasing cyanosis which would stimulate hyperpnea by virtue of the decreased arterial oxygen However on the basis of the work published by King and Franch and by Steeg and Hordof this diagram would have to be modified on the right side of the cycle to increased ratio of systemic to pulmonary flow In relation to hyperpnea I believe that Steeg and Hordof have confused hyperpnea with hyperventilation They state that hyperpnea cannot be implicated as the Pco remained constant Hyperpnea is not defined in terms of Pco in conditions of diminished pulmonary flow it is quite possible to have an increased ventilatory effort without a substantial reduction of CO or an increase in oxygen which is the important feature of these

Book reviews

Cleveland Clinic Cardiovascular Consultations Cardiovascular Clinics vol 7 no 1 Edited by A N Brest Philadelphia 1975 F A Davis Company 22? pages Price $23 00

This issue of Cardiovascular Clinics consists of a series of presentations of physicians from the Cleveland Clinic These papers summarize extremely well the experience and practice of these Cleveland Clinic physicians in the management of cardiovascular diseases The discussions are clearly presented and should interest all cardiologists and cardiovascular surgeons as well as all general physicians since the Cleveland Clinic group have been very active in this field for many years The papers are concerned with the common problems and especially two of the most common—arteriosclerosis and hypertension This volume of Cardiovascular Clinics is not only timely but adds important clinical information to the medical literature

Modern Cardiac Pacing Overview Edited by S Furman and D J W Escher Philadelphia 19?? Charles Press 314 pages

This book edited by Furman and Escher contains a series of relatively short chapters related to cardiac pacing Each chapter ends with a question and answer panel discussion The eleven chapters include practically all the general aspects of pacing the heart The electrophysiology of the His bundle non heart block pacing techniques temporary and permanent pacing atrial pacing atomic pacemakers and interference with pacemaker function are among the problems discussed This book is easy to read the type is large and the approach is practical The reader will find the panel discussions most interesting Pacing of the heart has been a definite advancement in cardiology and this book reviews the subject very well The book should interest all physicians and surgeons who are regularly treating cardiovascular diseases

The Electrocardiology of Coronary Artery Disease By Leo Schamroth, M D Philadelphia 1975 J B Lippincott Company 344 pages Price $23 00

The electrocardiogram is an extremely useful adjunct to the history and physical examination in the management of coronary artery disease However it must be made clear that it cannot stand alone Furthermore the changes in the electrocardiogram associated with cardiac disease are not always pathognomonic of coronary artery disease At times this reviewer has the impression from the text legends and illustrations that the author tends to lean toward that opinion too much The ECG changes in patients with coronary artery disease are not clearly understood or precise To wit on page 28? the legend to Fig 8? states that tall peaked T waves in V to V are due to a rind of subendocardial ischemia Was the patient followed to autopsy and where was the rind located or could it be located since the V to V exploring electrodes are placed over the right ventricle? Furthermore a rind of ischemia of the subepicardial surface layer of myocardium on the posterior wall of the left ventricle can produce high peaked T waves as shown in leads V to V of Fig 8? The tracing of Fig 5 may reflect left bundle branch block but it could also be produced by diffuse scarring with impairment of conduction in the Purkinje system. The evidence for subendocardial ischemia is not definite from the ECG Furthermore was the heart studied at autopsy? This is a good book, but QRS ST segment, and T wave changes found in the illustrations and described in the text can be produced by infection or toxic damage to the myocardium and scarring due to any cause This book is worth careful and critical study The mechanism for many of the ECG changes in coronary artery disease are yet to be explained There is no doubt that when the ECG is used in conjunction with clearly obtained clinical data it is extremely useful in the diagnosis and management of coronary artery disease It must be remembered it is disease of the myocardium and conduction tissue that produces the ECG alterations This is a useful and good book however

Advances in Beta adrenergic Blocking Therapy Sotalol Edited by Alan G Snart M D Amsterdam 1974 Excerpta Medica Price $45 95

As with all proceedings of international symposia this one consists of a collection of reports of presentations made at the meeting. The subject is an important one It is limited mainly to the β adrenergic blocking agent sotalol The principles of β adrenergic sympathetic nerve function is discussed along with the general effects of blocking this function The use of sotalol in pharmacology and physiology constitutes the main part of the publication Among the actions discussed are those related to hemodynamic myocardial and coronary arterial functions Obviously these discussions are applicable in general to all agents which block the β adrenergic nerve endings. This is a very good book on an important type of drug used in clinical practice

Coronary arteriography By Goffredo G Gensini, M D Mount Kisco New York 1975 Futura Publishing Company 498 pages.

Gensini has had many years experience in coronary angiography He reviews the history of the subject methods used technic and facilities necessary to do coronary arteriography and the details of data analysis storage and reporting This approach is practical precise and lucid His illustrations are excellent especially his presentations of coronary artery anatomy as reflected in the various views of the recorded angiograms. Students of coronary angiography will find this section to be extremely useful. The clinical applications of coronary angiography in medical and surgical care of patients is emphasized. The results of surgical bypass operations are also discussed and illustrated with tables and graphs This is a good book which should interest all cardiologists cardiac surgeons and those who do coronary angiography Beginners will learn a great deal from a study of Gensini's book

Encyclopedia of Medical Radiology Volume X part 2b Roentgen Diagnosis of the Heart and Blood Vessels Edited by H. Vieten Berlin 1974 Springer Verlag 554 pages

This tenth volume of a handbook on medical radiology presents in excellent and encyclopedic form discussions of cardiovascular radiology There are sections on cardiac coronary and pulmonary and systemic arterial and venous radiology The photographs are extremely clear and well selected The bibliography author and subject indices and printing are excellent. Cardiologists peripheral vascular physicians and cardiovascular surgeons as well as radiologists will find this volume to be very helpful in their practice and worth owning The whole series, but especially this volume should be translated into English It is an excellent addition to the handbook series on radiology

a role in sudden deaths during sexual activity Patients can easily stop physical activity when they suffer from precordial pain and they can also use nitrates when necessary But during the course of sexual activity they do not suffer from pain or discomfort because of sexual analgesia and therefore they tend to continue the sexual activity which in turn may result in a new myocardial infarction or sudden death

Istemi Nalbantgil M D
Ömer Yiğitbaşı M D
Bulent Kılıçcıoğlu M D
Ege University Medical School
Internal Medicine Clinic
Izmir Turkey

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Reply

To the Editor

Sexual analgesia as proposed by Drs Nalbantgil and associates certainly may be a contributory factor in coital sudden death However the two observations from which the analgesia hypothesis was derived deserve comment

The Holter monitor tracing demonstrating coital S T depressions was compared to the exercise electrocardiogram of the coronary patients Inability to standardize Holter monitors limits the value of the tracing to rate rhythm and conduction pattern analysis with S T and T wave changes being interpreted with caution because of distortion in the recording system and changes in the positional activity[1] Secondly onset of angina has been correlated with the heart rate × blood pressure product[2] The individuals described had a faster coital heart rate compared to the rate at the time exercise pain appeared Blood pressure recordings might put these data in proper perspective

Therefore while many conceive of coital death as a pleasant end I am not convinced that "death in the saddle" would be pain free

Andrew W Green M.D
State University of New York
at Buffalo
Department of Medicine
462 Grider St
Buffalo N Y 14215

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Editorial

Reciprocation: A mechanism for tachycardias

R. A. J. Spurrell, M.D., B.Sc., M.R.C.P., F.A.C.C.
London, England

Since programmed electrical stimulation of the heart has become a widely used technique for the investigation of arrhythmias, considerable interest has been shown in the underlying mechanism of various tachycardias and as a result a reciprocal or re-entry mechanism has been demonstrated as the underlying basis for many types of tachycardia. When we consider these advances in the last few years in the light of the arguments that have gone on for many years as to whether tachycardias are due to a rapidly discharging ectopic focus or some form of reciprocal mechanism, it gives rise to sobering thought to look back through the literature and find that as far back as 1913 Mines first coined the term "reciprocating rhythm."

That the supraventricular tachycardia associated with the Wolff-Parkinson-White syndrome is due to a reciprocal mechanism commonly involving antegrade conduction by way of the A-V node-His pathway with retrograde conduction by way of an accessory pathway was suggested by Holzmann and Scherf[2] years after the syndrome had been described by Wolff, Parkinson, and White. However, once again Mines had already demonstrated his advanced thinking in this field, for in 1914 he suggested that a reciprocal process involving antegrade conduction within the A-V node-His pathway and retrograde conduction by way of the A-V connection previously described by Kent might be responsible for producing a tachycardia. Today, 61 years later, after considerable controversy, the essentials of Mines' conclusions are accepted by most workers in this field.

As has been demonstrated in the Wolff-Parkinson-White (WPW) syndrome, the requirements for a reciprocal mechanism are two conduction pathways which differ in refractoriness and conduction velocity. Such pathways have been demonstrated in the A-V node by Mendez and Moe in 1966, and that a reciprocal or circus movement within the A-V node can produce a tachycardia has been demonstrated by Janse and associates. Their results have come from animal experimental work, but more recently intracardiac recordings and programmed electrical stimulation have supported the belief that a reciprocal mechanism within the A-V node forms the basis for many cases of supraventricular tachycardia.

Patients with paroxysmal supraventricular tachycardias due to a reciprocal mechanism may have both pathways of the reciprocal circuit in the A-V node, or the antegrade pathway may be in the A-V node while the retrograde pathway may be an accessory atrioventricular connection. It may be very difficult to say which of the two types of reciprocal circuit is being utilized when a patient presents with a supraventricular tachycardia, although the presence of a short retrograde conduction time (q-P interval) is suggestive of retrograde conduction occurring by way of an accessory pathway. If, when sinus rhythm is achieved, the sinus beats show pre-excitation (either a short PR interval or short PR interval and delta wave), then it is likely but not invariable that an accessory A-V pathway made up part of the reciprocal circuit. However, it is recognized that an accessory pathway may not conduct antegradely, or may only do so intermittently, and under these circumstances the diag-

From the Department of Cardiology, St. Bartholomew's Hospital, London, England.

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Reprint requests: R. A. J. Spurrell, M.D., Department of Cardiology, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, England.

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Human Endocrinology A Developmental Approach By Dorothy B Villee M D Philadelphia 1975 W B Saunders Company 453 pages.

Clinical Cardiology A Bedside Approach By Peter C Gazes, M D Chicago 1975 Year Book Medical Publishers, Inc., 318 pages

Cardiac Emergency Care Edited by Edward K Chung M D Philadelphia 1975 Lea & Febiger Publishers 371 pages

Announcements

Advances in cardiology

A three day symposium designed to present a comprehensive review and basic science background of the electrophysiologic basis for the diagnosis and treatment of clinical arrhythmias for the practicing physician including newer concepts in treatment will be presented at the Balboa Bay Club Newport Beach California April 1 through 3 1976 under the sponsorship of the Foundation for Cardiovascular Research and the Hospital of the Good Samaritan

Please direct all inquiries to the Foundation for Cardiovascular Research 39 Congress St Pasadena Calif 91105 Telephone (213) 792 4173

Symposium on postoperative pulmonary problems

A symposium entitled Postoperative Pulmonary Problems will be presented by The University of Texas Health Science Center at Houston Medical School and Division of Continuing Education on March 19 and 20 1976

The course will comprise an intensive review of the respiratory difficulties encountered by practicing physicians in the care of surgical patients It will include preoperative pulmonary evaluation pulmonary embolism prophylaxis and techniques of management of postoperative crisis such as atelectasis, pulmonary embolism respiratory failure and the adult respiratory distress syndrome One session will be devoted to the evaluation of patients for pulmonary resection The faculty will consist of guests and members of the departments of medicine pathology and surgery of The University of Texas Medical School at Houston Active participation by the course attendees will be encouraged in discussion of management challenges in individual case oriented fashion

For further information please contact The Office of the Director The University of Texas Health Science Center Division of Continuing Education P O Box 20367 Houston Texas 77025 Telephone (713) 792 4671

re-entrant loops within the Purkinje fiber system A reciprocal mechanism as the most likely basis for certain ventricular tachycardias in man has recently been demonstrated by Wellens and associates and using similar techniques others[20] have provided evidence that the reciprocal circuit in some patients may be of relatively large dimensions such as involving the main intraventricular bundle branch system More recently the site of the reciprocal circuit in the ventricles in man has been studied with epicardial mapping techniques[21,22] and following this surgical interruption of the reciprocal circuit has been carried out successfully It has become obvious from these studies that in man the precise localization of the reciprocal circuit in the ventricles and the relative parts played by the main intraventricular bundle branches the distal His Purkinje system and the ordinary working myocardium in the reciprocal circuit is extremely difficult to define mainly because of the limited number of epicardial myocardial and endocardial recording sites that can be simultaneously recorded during a ventricular tachycardia It is in this area that advances must be made during future clinical studies

In conclusion then it is now apparent that in many instances in man both supraventricular and ventricular tachycardias are due to a reciprocal mechanism The mechanism of action of antiarrhythmic drugs and the use of various pacing techniques for the management of reciprocal tachycardias are based on the proper understanding of the electrophysiologic properties of the reciprocal mechanism With the advent of surgical treatment for certain reciprocal tachycardias it has become essential to understand not only the electrophysiologic mechanism of reciprocation but also the precise anatomic localization of the conduction pathways involved in the various reciprocal circuits

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nosis of pre excitation during sinus rhythm may be *impossible*. This therefore raises the question whether a proportion of patients with apparent *intra-A V nodal reciprocal tachycardias may, in fact, have a* concealed accessory A-V pathway which only functions for retrograde conduction during tachycardia. Spurrell and associates[11] studied 13 patients with paroxysmal supraventricular tachycardia who showed no evidence of pre-excitation on the resting electrocardiogram but in five of the patients ventricular stimulation studies and the administration of the drug verapamil suggested that a concealed accessory A V pathway was used for retrograde conduction during a reciprocal tachycardia. More recently Narula[1] using similar techniques demonstrated in a group of patients the presence of retrograde pre excitation in the absence of antegrade pre excitation and suggested that this may be due to a concealed accessory A V pathway.

Other techniques used in order to localize the site of the retrograde pathway during a reciprocal tachycardia involve the positioning of recording electrodes in the right atrium and either the left atrium or the coronary sinus in order to record left atrial activity in the region of the left A V groove. Massumi and associates[13] have shown that in patients with normal conduction systems during right ventricular pacing the sequence of retrograde atrial activation by way of the A V node His pathway is such that either right and left atrial activation occur simultaneously or right atrial activation occurs up to 30 msec before left atrial activation. In our laboratory we have obtained a similar sequence of retrograde atrial activation during reciprocal supraventricular tachycardia in patients with intra-A V nodal reciprocation and the supraventricular tachycardia associated with the type B WPW syndrome (right sided accessory pathway) where as in patients with type A WPW (classically a left sided accessory pathway) where as in patients with type A WPW during reciprocal tachycardia retrograde left atrial activation occurs before right atrial activation.[14] These latter findings are supported by Wallace and associates.[15] Usually, therefore the presence of retrograde right atrial activation occurring before retrograde left atrial activation during a reciprocal supraventricular tachycardia would lead one to suspect either a reciprocal circuit in which both the antegrade and retrograde pathways occur within the A V node or a reciprocal circuit in which the antegrade pathway occurs within the A V node His system and retrograde conduction is by way of an accessory pathway inserting into the right atrium as in the type B WPW syndrome. Retrograde left atrial activation occurring before retrograde right atrial activation during supraventricular tachycardia would lead one to suspect that retrograde conduction was occurring by way of a left sided accessory A V pathway as in the type A WPW syndrome. Two patients studied recently in our own laboratory (unpublished data) had however, no evidence of pre excitation during sinus rhythm but during reciprocal supraventricular tachycardia retrograde left atrial activation as recorded in the distal coronary sinus occurred well before the right atrial activation suggesting the presence of a concealed left sided accessory pathway which functioned only for retrograde conduction. A word of caution should be sounded here. Scherf and Cohen[16] emphasized the presence of left atrial as well as right atrial connections of the A V node. Theoretically therefore a supraventricular tachycardia due to intra-A V nodal reciprocation could use a part of the A V node which has left atrial connections for retrograde conduction and under these circumstances retrograde left atrial activation would be expected to occur before right. Care must therefore be taken in assessing the significance of electrophysiologic data in terms of deciding whether a supraventricular tachycardia is due to total intra-A V nodal reciprocation but with early retrograde left atrial activation or due to reciprocation involving antegrade conduction in the A V node His pathway and retrograde conduction in a left sided accessory A V pathway possibly close to the A V junction of the sort found in some types of the WPW type A. This has been demonstrated by Wellens and associates[17] who considered that in two out of four patients with type A WPW syndrome who underwent surgery the left sided accessory A V pathway might be closely adjacent to the A V junction. Careful electrophysiologic assessment therefore becomes increasingly important today since the techniques are now available for surgical interruption of accessory A V pathways necessitating the precise *localization* of such pathways.

A considerable amount of evidence has accrued to support a reciprocal mechanism as the basis for many ventricular arrhythmias. This has recently been discussed by Wit and associates[18] *in terms of*

re-entrant loops within the Purkinje fiber system A reciprocal mechanism as the most likely basis for certain ventricular tachycardias in man has recently been demonstrated by Wellens and associates[19] and using similar techniques others[20] have provided evidence that the reciprocal circuit in some patients may be of relatively large dimensions such as involving the main intraventricular bundle branch system More recently the site of the reciprocal circuit in the ventricles in man has been studied with epicardial mapping techniques[21, 22] and following this surgical interruption of the reciprocal circuit has been carried out successfully It has become obvious from these studies that in man the precise localization of the reciprocal circuit in the ventricles and the relative parts played by the main intraventricular bundle branches the distal His Purkinje system and the ordinary working myocardium in the reciprocal circuit is extremely difficult to define mainly because of the limited number of epicardial myocardial and endocardial recording sites that can be simultaneously recorded during a ventricular tachycardia it is in this area that advances must be made during future clinical studies

In conclusion then it is now apparent that in many instances in man both supraventricular and ventricular tachycardias are due to a reciprocal mechanism The mechanism of action of antiarrhythmic drugs and the use of various pacing techniques for the management of reciprocal tachycardias are based on the proper understanding of the electrophysiologic properties of the reciprocal mechanism With the advent of surgical treatment for certain reciprocal tachycardias it has become essential to understand not only the electrophysiologic mechanism of reciprocation but also the precise anatomic localization of the conduction pathways involved in the various reciprocal circuits

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Clinical communications

Primary risk factors in patients with myocardial infarction

Dag Elmfeldt, M D
Lars Wilhelmsen, M D
Hans Wedel, Ph D
Anders Vedin M D
Claes Wilhelmsson M D
Gosta Tibblin, M D
Goteborg Sweden

Most prospective epidemiological studies have shown significant relationships between myocardial infarction and the level of serum cholesterol blood pressure, and smoking and that these factors increase the risk independently [1,2] Increasing age, male sex, diabetes, and some other factors have also been associated with increased risk of suffering myocardial infarction It has also been shown that approximately 50 per cent of cases of coronary heart disease have relatively low predicted risk based on serum cholesterol systolic blood pressure and smoking [3] This and other findings have led to the assumption that there are other hitherto undefined factors associated with coronary heart disease

Prospective studies are generally most suitable for detection of risk factors This type of study is however, very time consuming and expensive and is therefore not suitable for research aimed at developing new hypotheses A group of individuals who have already suffered the disease may be chosen instead but the disease may alter certain factors, for example, the blood pressure after myocardial infarction, and the patients may be selected, for example due to death The advantage of studying patients who already suffer from the disease is that a sufficiently large series of patients can be relatively rapidly collected for study even of variables which occur with low frequency and probably have varying significance in different age groups

The aim of the present investigation was to study the distribution of retrospectively allocated risk among men who had survived a myocardial infarction and to compare these patients with random population samples It was also planned to analyze in detail patients who had a relatively low predicted probability of myocardial infarction in order to identify any variables not included in the risk function that might 'explain why these patients had suffered myocardial infarction Thus, the following variables were studied Registration by a Temperance Board low physical activity at work and during leisure time, psychological stress, diabetes gallstone kidney stone dyspnea on exertion, and triglycerides

Study population and methods

Since Jan 1 1968 all cases of acute myocardial infarction occurring in the population of Goteborg in certain age groups have been registered by a special organization [4] The registration comprised 90 per cent of all surviving diagnosed cases of myocardial infarction in Goteborg in the age groups concerned Patients discharged from hospital alive have been systematically followed up at a special clinic—The Post Myocardial Infarction Clinic [5,6] During the years 1968 69 all patients aged 55 years or below were included and in 1970 all patients aged 67 years or below were included with the exception of a randomly selected 30 per cent sample in the age group 57 67

From the Section of Preventive Cardiology Department of Medicine I Sahlgren s Hospital S 413 45 Göteborg Sweden

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Reprint requests Lars Wilhelmsen M D Department of Medicine I Sahlgren s Hospital S 413 45 Göteborg Sweden

years which was omitted in order to form a control group A total of 299 men with *primary* infarction were cared for during the years 1968 to 1970

It has been shown that serum cholesterol and blood pressure as well as smoking habits change with myocardial infarction but studies of a population sample examined before as well as after a myocardial infarction gave us the possibility of predicting certain of these changes Thus it was possible to retrospectively predict the probability (p) of suffering a myocardial infarction for the infarction patients of the present study This was done with aid of a multiple risk function developed from a multivariate logistic analysis by Wilhelmsen Wedel and Tibblin[3] This function gives the predicted probability for a 50 year old man to suffer a myocardial infarction during 9 years and 4 months follow up The predicted probability will hereafter be called the risk The risk function was based on the factors serum cholesterol systolic blood pressure and tobacco smoking For easy practical work nomograms of the risk function were constructed for various tobacco consumption as follows "never smoked" "ex smokers" "smoke 1 to 14 Gm daily" "smoke 15 to 24 Gm daily" and "smoke > 25 Gm daily" with serum cholesterol and systolic blood pressure on the horizontal and vertical axes respectively (Fig 1)

Smoking habits prior to the infarction according to interview were used According to earlier experiences, serum cholesterol has usually returned to preinfarction levels about 3 months after the infarction[7] which is why these values were used Since blood pressure has been shown to fall in connection with a myocardial infarction and this reduction of blood pressure cannot at present be predicted two blood pressure groups were created One group consisted of probable hypertensive patients and the other group of probable nonhypertensive patients The group of probable hypertensive patients consisted of individuals who had been treated for hypertension prior to infarction or who had manifest hypertension during the first year of follow up defined as systolic blood pressure > 160 mm Hg and/or diastolic blood pressure > 105 mm Hg for patients up to 55 years of age and diastolic pressure > 105 mm Hg for patients above this age In order to fulfill the criterion for manifest hypertension two consecutive determinations per-

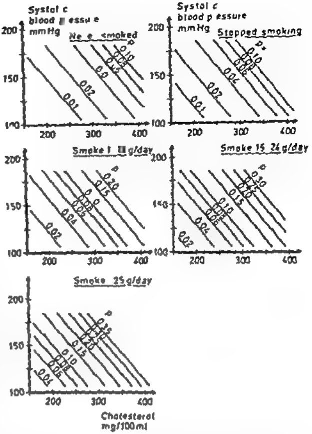

Fig 1 Nomograms for determination of predicted probability (p) of a 50-year-old man without clinical signs of coronary heart disease suffering myocardial infarction before the age of 60 years. (According to Wilhelmsen Wedel and Tibblin Circulation 48 950 1973.)

formed within 2 to 4 weeks were to give the above values Determination of the blood pressure was performed in accordance with WHO's recommendations.[1] On the basis of the mean blood pressure value for hypertension obtained in a primary preventive trial concerning cardiovascular disease and comprising 7 455 men examined in an intervention group[12] the patients considered probably to be hypertensive were allocated a systolic blood pressure of 170 mm Hg The remaining patients were placed in the probably nonhypertensive group and allotted a systolic blood pressure of 150 mm Hg which was the mean value for persons without known hypertension in the primary preventive trial Some bias was evidently introduced by this type of allocation to two groups but by studying Fig 1 it can be seen that the possible bias is acceptable

For 270 of the 299 men who had survived their first infarctions complete details concerning

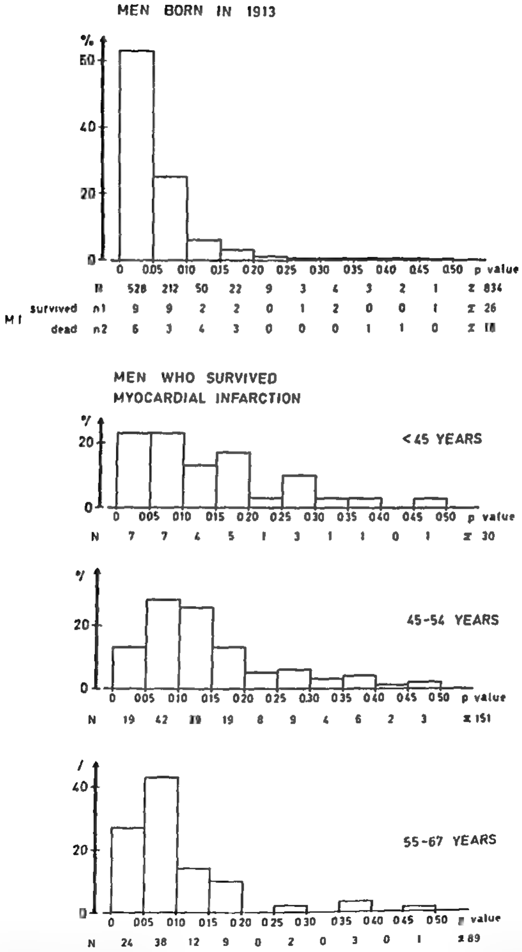

Fig 2 Distribution of predicted probability (p value) of myocardial infarction for a population sample (men born in 1913) and for a representative series of men who survived myocardial infarction The number of cases of infarction occurring during 9 years and 4 months follow up of the population sample is denoted

Table I Per cent distribution of certain variables by risk and age in men who survived myocardial infarction compared to random population samples of men

Risk (p)	Men with infarction (45 yr)			Population (50 yr)	Men with infarction (45 54 yr)			Population (62 yr)	Men with infarction (55 67 yr)		
	0 10	0 10-0 19	0.20		0 10	0 10 0 19	0.20		0 10	0 10-0 19	0.20
No	14 (%)	10 (%)	6 (%)	855 901† (%)	60 (%)	62 (%)	29 (%)	95 (%)	62 (%)	21 (%)	6 (%)
Registered by Temp Board	21	30	[illegible]	21	13	21	11	27			
Low physical activity at work (1 2 points)	60	[illegible]	25	68†	76	69	76	[illegible]	87	57	67
Low physical activity during leisure time (1 2 points)	80	67	100	84†	92	98	84	92	92	86	[illegible]
Stress (5-6 points)	43	70	17	14†	45	38	25	11			
Diabetes	14	[illegible]	0	2†	7	2	0	2	7	5	[illegible]
Gallstone	14	10	0	5	12	11	14	6	15	14	[illegible]
Kidney stone	[illegible]	20	33	7	20	11	14	7	24	0	17
Dyspnea on exertion	50	30	16	23	32	39	38	33	76	81	100

Men born in 1913.
†Men from the primary preventive trial.

Table II Serum triglycerides (mg /100 ml.) by risk and age in men who survived myocardial infarction compared to male population samples

Risk (p)	Men with infarction (45 yr)			Normal population (50 yr) 853	Men with infarction (45-54 yr)			Normal population (62 yr) 91	Men with infarction (55 67 yr)		
	0 10	0 10-0 19	0.20		0 10	0 10 0 19	0.20		0 10	0 10-0 19	0.20
N	14	10	6		60	59	27		60	20	6
Triglycerides											
Mean	146	143	197	108	138	158	197	140	157	153	318
S D	59	64	48	65	50	88	65	112	63	56	281

Men born in 1913.

serum cholesterol systolic blood pressure and tobacco smoking were available Eleven men had died within 3 months after the infarction and in 18 cases information on one of the variables of the risk function was lacking

The 270 patients were allocated a risk (p) in accordance with the nomograms The patients were arbitrarily allocated to one of the three groups according to risk $p < 0.10$ $p = 0.10$ to 0.19 and $p \geq 0.20$

Certain variables were compared in the patient series and in representative population samples of men aged 50 and 62 years respectively Data for 50-year-old men were taken either from the study of "Men born in 1913" or from one age group of men in the primary preventive trial.[15] The first study comprised 855 men born in 1913 and examined in 1963 They included 88 per cent of all men registered in Goteborg and born on dates which are even multiples of 3 i.e., 3 6 9 12 etc The men from the primary preventive trial were a randomly selected third of persons born in 1921 of whom 80 per cent or 901 men participated in the examination.[16] One or the other of the groups of 50-year old men was chosen depending on availability of data The 62 year old men consisted of men registered in Goteborg and born in 1906 on the fifteenth or thirtieth day of each month They participated in a cross sectional study performed in 1972 and comprising 96 individuals A description of the study and an analysis of nonparticipants have been presented previously.[17]

Both the patients and the population sample were investigated and interviewed according to

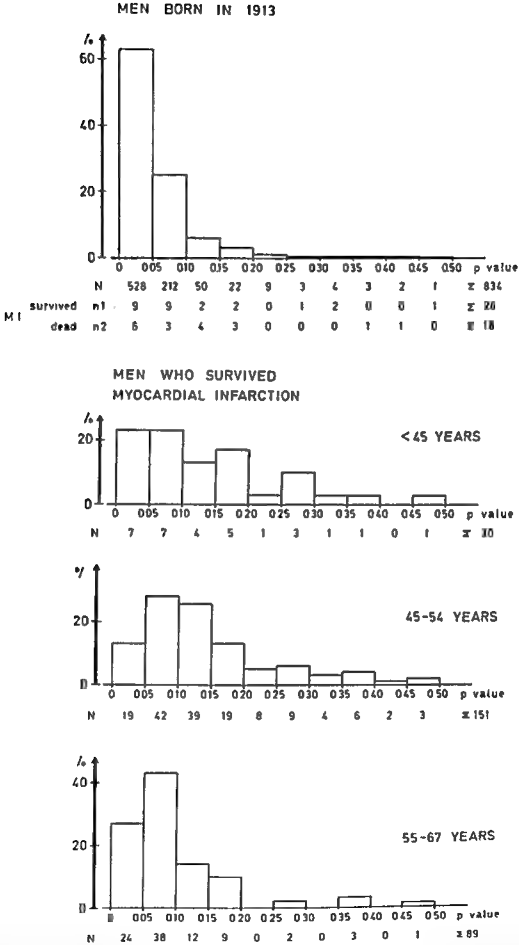

Fig 2 Distribution of predicted probability (p value) of myocardial infarction for a population sample (men born in 1913) and for a representative series of men who survived myocardial infarction The number of cases of infarction occurring during 9 years and 4 months follow up of the population sample is denoted

of patients with dyspnea upon exertion to increase with increasing risk

The triglycerides in the patient group with low risk in the age group 45 to 54 years were higher than in the population sample (138 and 108 mg per 100 ml respectively) In the age group below 45 years the triglycerides in the lowest risk group were also much higher than expected in the corresponding age in the population sample The same was true for the age group 55 to 67 years

Discussion

In the prospective studies of suspected risk factors difficulties have been encountered in assessing the importance of factors which occur infrequently in the population This is for example true of diabetes though there is a great deal of clinical evidence suggesting that this disease carries an increased risk of ischemic heart disease A representative large material of infarction patients in a defined population gives greater possibilities of studying factors which occur with low frequency and which may be associated with an increased risk of infarction

The significance of the 10 per cent dropouts among the patients is a matter of conjecture None of the variables included in the risk function the risk factors has been shown to be of importance for death during the first 3 months after an infarction The deletion of the 11 subjects who died within 3 months can therefore not have any great influence on the results For the 18 individuals for whom information on one of the variables included in the risk function was lacking a special analysis was performed It was found that they did not differ systematically with respect to existing variables from the remaining 270 infarction patients

The minor significance of the dropouts and the justifiability of the method used have been confirmed by a special analysis The representative population sample of 50 year old men was added to the patients in the age group 45 to 54 years. The multiple risk function was applied to the composite material and the good predictability was confirmed There was no tendency toward concentration of patients from either of the original groups in any particular risk area

In the present study it has been shown that a not inconsiderable number of patients have suffered myocardial infarction despite relatively low risk ($p < 0.10$) according to the multiple risk function It is improbable that this is essentially due to the fact that the function is based on a single observation of the variables included—serum cholesterol systolic blood pressure and tobacco smoking Whether or not repeated data with respect to these three variables would give a significant improvement in predictability is not known but is of course an interesting question It is more probable however that several other factors perhaps not yet studied are of great importance for the risk of suffering infarction

The results of this study strongly suggest that mental stress diabetes dyspnea upon exertion and raised serum triglycerides partly explain the occurrence of infarction in patients with low risk ($p < 0.10$) who survive myocardial infarction at least in the age groups up to 54 years In addition low physical activity during leisure time may be of some importance It is possible that the stress variable used is associated with type of personality "life changes etc but the latter variables require further study It must be emphasized that the variable mental stress is sensitive to the retrospective method used during the interview of the patients

The same criticism against the retrospective method may apply to the evaluation of physical activity and possibly also to dyspnea on exertion

A high prevalence of diabetes in patients who survive myocardial infarction whether the case history or a pathological oral or intravenous glucose tolerance test is used as the diagnostic criterion has been reported in a large number of studies during more than 30 years [11 2] Prospective studies have shown that diabetic patients or persons with asymptomatic hyperglycemia have a higher incidence of ischemic heart disease than those without diabetes [21 2] This higher incidence has been particularly pronounced in persons who also have high blood pressure [3]

Dyspnea on exertion was in all age groups more common among the patients than in the population sample which has been reported in more detail in another paper [11] In the youngest patients the occurrence of dyspnea decreased with increasing risk which suggests that dyspnea is an independent risk factor which was also shown in multivariate analyses by Wilhelmsen and associates.[2] In older patients however the occurrence of dyspnea increased with increasing risk It is possible that the significance of dyspnea varies in

standardized methods[11-13] The variables subjected to special study in the present investigation were the following registration by the Temperance Board, physical activity during work and leisure time mental stress, diabetes, gall stone, kidney stone, dyspnea, and serum triglycerides Information was obtained from the Temperance Board in Goteborg as to whether or not the person in question was known to the Board in connection with intemperance Physical activity was estimated on a four point scale Low physical activity was considered to be present for subjects allocated one or two points[14] Mental stress was operationally defined according to a six point scale a high degree of stress corresponding to the constant experience of stress during the past year (five points) or past 5 years (six points) Diabetes, gallstone and kidney stone were considered to be present in subjects who had been informed by a physician that they had the condition concerned Dyspnea was considered to be present when the subject reported breathlessness when walking rapidly on level ground or climbing a small hill (or upon less exertion) For the infarction patients the history concerned the time *before* their infarction Triglycerides were analyzed according to a method described by Carlson[15]

Results

Fig 2 shows the distribution of risk for suffering myocardial infarction according to the multiple risk function for a representative sample of men—'Men born in 1913'—and for the 270 men with primary infarctions divided into three age groups The figure also shows the number of cases of infarction during 9 years and 4 months of follow up among men from the population sample Low risk defined as $p < 0.10$ was found in 88 per cent of the population sample In the infarction patients there was a definite tendency to higher risk than in the population but $p < 0.10$ was found in 46 per cent of men below age 45 years 41 per cent among patients aged 45 to 54 years, and 70 per cent in patients aged 55 to 67 years Thus a tendency to lower risk according to these variables was found among infarction patients in the highest age group as compared to lower age groups

Table I shows the distribution of some variables, which were not included in the risk function The values for serum triglycerides are shown in Table II In the three age groups patients with low ($p < 0.10$), moderate ($p = 0.10$ to 0.19) and high risk ($p > 0.20$) are analyzed For the infarction patients aged 45 to 54 years the biggest population samples are available In this age group registration by the Temperance Board was less common among surviving patients than in the 50 year old population sample There was no tendency toward a continuously increased or decreased proportion of individuals registered by the Temperance Board between the risk groups of patients Low physical activity at work was somewhat more common among patients but there was no tendency toward differences between the risk groups Low activity during leisure time was more common among the patients but there was no tendency toward differences between the risk groups As regards stress the patient group as a whole was more exposed to stress than the population sample and there was a tendency for those with the lowest risk to contain the highest proportion of patients with a high degree of stress (45 per cent) and those with the highest risk to have the lowest proportion of patients with high degree of stress (25 per cent) The same relationship was found for diabetes which was found in 7 per cent of the patients with the lowest risk, whereas none of the patients with the highest risk had diabetes Gallstone and kidney stone were more common among the patients than in the population However, there was no tendency toward a continuously increased or decreased proportion of individuals with gallstone or kidney stone between the risk groups The situation was the same with respect to dyspnea upon exertion

For patients in the age group below 45 years it is difficult to draw conclusions due to the small numbers of patients in the different risk groups and the lack of reference groups It is worthy of note however, that a high degree of stress showed the same distribution tendency as in the age group 45 to 54 years and that diabetes and gall stone as well as dyspnea upon exertion occurred more frequently than in the population of 50 year old men These variables were more common among patients with low risk than among those with high risk

Diabetes, gallstone, and kidney stone were also found more frequently than expected in the age group 55 to 67 years particularly in the low risk group Dyspnea was found considerably more often among the patients than in the population sample There was a tendency for the proportion

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Results

Fig 2 shows the distribution of risk for suffering myocardial infarction according to the multiple risk function for a representative sample of men— Men born in 1913'—and for the 270 men with primary infarctions divided into three age groups The figure also shows the number of cases of infarction during 8 years and 4 months of follow up among men from the population sample Low risk, defined as $p < 0\ 10$ was found in 88 per cent of the population sample In the infarction patients there was a definite tendency to higher risk than in the population, but $p < 0\ 10$ was found in 46 per cent of men below age 45 years 41 per cent among patients aged 45 to 54 years, and 70 per cent in patients aged 55 to 67 years Thus, a tendency to lower risk according to these variables was found among infarction patients in the highest age group as compared to lower age groups

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different ages A methodological source of bias may be suspected Thus, patients may not be able to differentiate between angina pectoris and dyspnea Patients and men in the population samples were, however, interviewed by the same physicians and they were aware of this problem In most cases the chest symptoms could not be classified as angina pectoris but as dyspnea The high prevalence of dyspnea among patients in the present study may partly be explained by the fact that a majority of patients were smokers and somewhat less physically active Dyspnea has, however, been shown, by multivariate analyses to be associated with an increased risk of myocardial infarction, irrespective of other risk factors[2] The finding may be explained by the fact that dyspnea is a symptom of myocardial disturbance, even prior to infarction This may be due to either ischemia or to some other at present unknown, factor[32]

As regards serum triglyceride values these varied in parallel with the risk function, so that high risk was associated with higher triglyceride values This was in principle true for all three age groups and may partly be explained by the correlation between cholesterol and triglycerides[2] In the multivariate analyses it was also found that inclusion of serum triglyceride did not improve the possibilities of prediction in these middle aged men[2]

There are evidently other factors which could have been studied in addition to those mentioned in the present paper Thus we were interested in finding any useful data indicating a genetic predisposition to coronary heart disease It turned out, however, that the knowledge of parents cause of death was limited In a prospective study there was, however, found a tendency for earlier death among parents of those who later suffered myocardial infarction[33]

It should be observed that the results of the present study are based on an analysis of surviving male patients Other factors may be of importance for, or be associated with, increased risk of dying of ischemic heart disease An example of this is the finding that alcoholic problems occurred more frequently among men with fatal than those with nonfatal myocardial infarction[17]

Summary

A predicted probability of suffering myocardial infarction based on a multiple risk function involving serum cholesterol, systolic blood pressure, and tobacco consumption, was allocated retrospectively to 270 men who survived a primary myocardial infarction The infarction patients were representative of all surviving, diagnosed cases of primary infarction in men in certain age groups in Göteborg, Sweden, during the years 1968 70 The patients were divided into three groups—low, moderate and high risk A large number of patients had suffered infarction despite relatively low risk but the patients showed a tendency toward higher risk in comparison with the risk distribution in a representative population sample In order to study whether other variables not included in the risk function could "explain" the infarction in patients with relatively low risk, the different risk groups were compared A high degree of mental stress diabetes mellitus, and dyspnea on exertion, and possibly also raised triglycerides contributed to "explain" the infarctions in the low risk group Low physical activity during leisure time was probably also of importance

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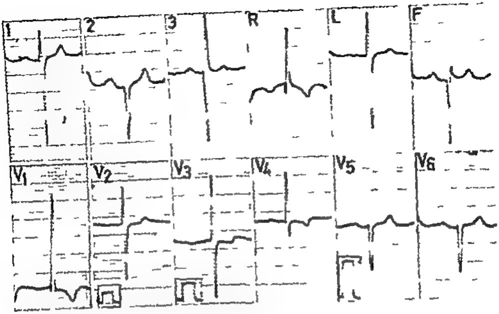

Fig 1 ECG in a case of constrictive pericarditis with subpulmonic annular constriction showing marked right axis deviation and severe right ventricular hypertrophy Right ventricular pressure 160 mm Hg

and angiographic findings were available and these confirmed the presence of pericardial constriction For this group the average mean pressures were right atrium 18 mm Hg pulmonary artery 29 mm Hg pulmonary capillary wedge pressure 20 mm Hg In no case did the difference between left and right atrial pressures exceed 6 mm Hg The mean cardiac index in these 69 cases was 2 8 L /min /M² Angiography showed normal ventricular contractility with a characteristic abrupt halt in diastolic filling

Results

Following scrutiny of the ECG s the material was divided into two groups

Group A 116 tracings compatible with constrictive pericarditis (95 per cent) The mean QRS axis was normal in one case the axis was –30 and in 115 it was between 0 and 90° Generalized T wave flattening or inversion was present in every instance The voltage was decreased in 103 (89 per cent) and normal in 13 Sinus rhythm was present in 108 (93 per cent) and atrial fibrillation in eight Left atrial enlargement was present in 36 cases (31 per cent)

Cardiac catheterization data were available in 63 of the 116 cases and in none was there evidence of mitral pulmonic or aortic stenosis suggestive of annular constriction

Group B Six tracings showing right axis deviation or right ventricular hypertrophy or both (5 per cent) Six cases (5 per cent) showed evidence of right ventricular hypertrophy with a dominant R wave in V_1 and reversal of the R/S ratio three tracings showed right axis deviation in addition T wave flattening or inversion over precordial leads V_{1-4} was present in all six tracings Sinus rhythm was present in five and atrial flutter in one Four cases had evidence of left atrial enlargement

Cardiac catheterization data were available in all six cases In one patient who presented in right ventricular failure the right ventricular pressure was 160 mm Hg with pulsus alternans as a result of fibrous, noncalcific subpulmonic annular constriction the ECG showed an axis of +210° and was compatible with severe right ventricular hypertrophy (Fig 1) This patient died following pericardiectomy and relief of the outflow tract obstruction Another patient whose ECG also showed right axis deviation and right ventricular hypertrophy refused operative management the hemodynamic data in this case were comparable to those in the 63 catheterized cases in Group A and there was no evidence to suggest annular constriction (Fig 2)

Of the remaining four patients who had evidence of right ventricular hypertrophy one showed additional right axis deviation Their

The ECG of constrictive pericarditis—Pattern resembling right ventricular hypertrophy

Elliot Chesler, M D, F R C P F A C C
Abdul S Mitha, M R C P (Lond)
Rodney E Matisonn M B Ch B F C P (S A)
Durban South Africa

Even in the subacute phase of constrictive pericarditis where the heart is large and may simulate cardiomyopathy, the correct diagnosis can almost invariably be made by careful clinical evaluation at the bedside In regions where constrictive pericarditis and cardiomyopathy are prevalent, this diagnostic problem frequently arises and a great deal of reliance is placed upon the electrocardiogram (ECG)

In constrictive pericarditis the ECG shows classic abnormalities in at least 90 per cent of cases but may be normal in the remainder Characteristically the QRS vector is normally directed with low voltage and there is widespread flattening or inversion of the T wave [1] Authoritative textbooks[2, 3] have stated however that the occasional tracing may show right axis deviation and right ventricular hypertrophy—a pattern which has also been noted in association with annular pericardial constriction [4]

In our experience we have also encountered cases of constrictive pericarditis where the ECG has shown unexpected evidence of right ventricular hypertrophy The frequency of this confusing finding has not been documented or explained and this is the subject of this paper

Patients and Methods

The material consists of 122 patients with constrictive pericarditis in whom an operation was undertaken in all but one Eighty eight were male, 34 were female and their average age was 33 years 113 (93 per cent) were African, five Caucasian three Mulatto and one Asiatic The etiology was tuberculous in all except six, in whom the cause was pyogenic in four and a result of amebiasis in the remaining two

Because of the virulence of tuberculosis in the African population the majority of our patients present with constriction in the subacute stage of the disease [5] Typically there is cardiomegaly and persistent pleural effusion, whereas pericardial calcification and atrial fibrillation are present in only 11 and 7 per cent of cases, respectively At operation the two layers of the pericardium are usually separated by fluid or caseous material and constriction is caused by thickened fibrotic visceral pericardium This is in contrast to the experience in Caucasians of whom 75 per cent present in the chronic state with a near normal heart size, pericardial calcification in 70 per cent and atrial fibrillation in 35 per cent [1]

Twelve lead ECG s were available in all cases and in most instances serial tracings were obtained In all cases particular attention was paid to the QRS voltage and the mean axis was plotted to within the nearest 10 degrees of the hexaxial reference system Right ventricular hypertrophy was diagnosed when there was reversal of the ratio of R/S in V_1 to V_5 (R/S = > 1) and right axis deviation when the mean QRS was deviated to the right of +100° Left atrial enlargement was diagnosed when there was terminal negativity of the P wave of 1 mm or more in depth with duration of 0 04 second or more in Lead V_1

In 69 of the 122 cases cardiac catheterization

From the Cardiac Unit Wentworth Hospital and the University of Natal Durban South Africa

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Reprint requests Professor E Chesler Cardiac Unit Wentworth Hospital P B Jacobs Natal 40 6 Durban South Africa

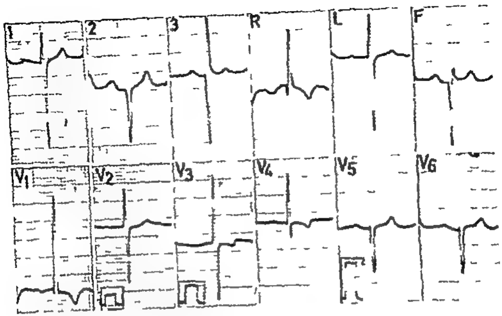

Fig 1 ECG in a case of constrictive pericarditis with subpulmonic annular constriction showing marked right axis deviation and severe right ventricular hypertrophy Right ventricular pressure 160 mm Hg.

and angiographic findings were available and these confirmed the presence of pericardial constriction For this group the average mean pressures were right atrium 18 mm Hg pulmonary artery 29 mm Hg pulmonary capillary wedge pressure 20 mm Hg In no case did the difference between left and right atrial pressures exceed 6 mm Hg The mean cardiac index in these 69 cases was 2 8 L/min/M² Angiography showed normal ventricular contractility with a characteristic abrupt halt in diastolic filling

Results

Following scrutiny of the ECG s the material was divided into two groups

Group A 116 tracings compatible with constrictive pericarditis (95 per cent) The mean QRS axis was normal in one case the axis was −30° and in 115 it was between 0 and 90 Generalized T wave flattening or inversion was present in every instance The voltage was decreased in 103 (89 per cent) and normal in 13 Sinus rhythm was present in 108 (93 per cent) and atrial fibrillation in eight Left atrial enlargement was present in 36 cases (31 per cent)

Cardiac catheterization data were available in 63 of the 116 cases and in none was there evidence of mitral pulmonic or aortic stenosis suggestive of annular constriction

Group B Six tracings showing right axis deviation or right ventricular hypertrophy or both (5 per cent) Six cases (5 per cent) showed evidence of right ventricular hypertrophy with a dominant R wave in V_1 and reversal of the R/S ratio three tracings showed right axis deviation in addition T wave flattening or inversion over precordial leads V_1 was present in all six tracings Sinus rhythm was present in five and atrial flutter in one Four cases had evidence of left atrial enlargement

Cardiac catheterization data were available in all six cases In one patient who presented in right ventricular failure the right ventricular pressure was 160 mm Hg with pulsus alternans as a result of fibrous noncalcific subpulmonic annular constriction the ECG showed an axis of +210° and was compatible with severe right ventricular hypertrophy (Fig 1) This patient died following pericardiectomy and relief of the outflow tract obstruction Another patient whose ECG also showed right axis deviation and right ventricular hypertrophy refused operative management the hemodynamic data in this case were comparable to those in the 63 catheterized cases in Group A and there was no evidence to suggest annular constriction (Fig 2)

Of the remaining four patients who had evidence of right ventricular hypertrophy one showed additional right axis deviation Their

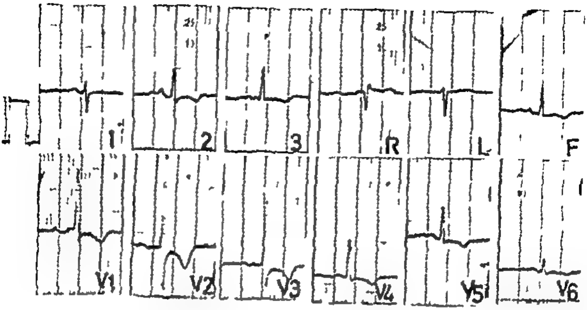

Fig 2 ECG in a case of constrictive pericarditis showing sinus rhythm right axis deviation (+120) marked right ventricular hypertrophy *with generalized T wave flattening and inversion Right ventricular pressure 60 mm Hg*

Fig 3 ECG s in a case of constrictive pericarditis The preoperative tracing (*A*) shows right axis deviation (+110) and a dominant R in Lead V Right ventricular pressure 45 mm Hg A normal R/S ratio in V is present after operation (*B*)

hemodynamics were also typical of constrictive pericarditis without annular constriction Following pericardiectomy the QRS axis returned to normal and the evidence of right ventricular hypertrophy regressed (Figs 3 and 4)

Comment

Of the 122 ECG's in this study 95 per cent were compatible with constrictive pericarditis characteristically showing a normally directed QRS axis and widespread T wave inversion or flattening

Fig 4 ECGs in a case of constrictive pericarditis The preoperative tracing (*A*) shows sinus rhythm and a normal frontal plane axis with pattern compatible with right ventricular hypertrophy Right ventricular pressure 49 mm Hg The R/S ratio in V and V reverts to normal after operation (*B*)

with low voltage in the majority These findings are very helpful in the distinction from congestive cardiomyopathy which may mimic constrictive pericarditis in the subacute stage In congestive cardiomyopathy the ECG shows a fairly uniform pattern of left ventricular hypertrophy conduction defects involving the left bundle occur in 25 per cent of cases and left bundle branch block and left anterior hemiblock occur with equal frequency[6] The normal QRS axis in constrictive pericarditis is also a useful diagnostic point in those cases of constrictive pericarditis which resemble rheumatic mitral stenosis Both conditions may present with mid diastolic murmurs left atrial enlargement or atrial fibrillation however in patients with mitral stenosis and P mitrale the mean QRS axis is frequently deviated to the right

The presence of right axis deviation and right ventricular hypertrophy in constrictive pericarditis has been noted by Schrire and by Fowler[2] but the frequency and mechanism were not stated In our study we observed these findings in six cases (5 per cent) and in only one with subpulmonic stenosis and a right ventricular pressure of 160 mm Hg could we find a ready explanation Pericarditis is an unusual cause of obstruction to the right ventricular outflow tract and was first described by Mounsey[4] In the five cases we have found reported in the literature comment on the ECG was available in four and all showed right axis deviation and right ventricular hypertrophy It is of interest that whereas four of these cases had previous inadequate pericardiectomies the fifth like our case had no previous operation[4, 8, 11]

It is unlikely however that all the examples of right axis deviation and right ventricular hypertrophy noticed by other observers can be explained on the basis of subpulmonic stenosis alone Thus in five of our six cases there was no evidence of annular constriction hemodynamically or angiographically, nor was this identified surgically

The usual causes of a dominant R wave in Lead V_1 are pulmonary hypertension, Wolff Parkinson White syndrome, and true posterior infarction, none of which can reasonably be invoked as an explanation in these cases[1] Similarly, right axis deviation resulting from posterior hemiblock is unlikely since the subendocardium of the left ventricle is not involved by pericarditis The fact that myocardial hypertrophy has never been demonstrated pathologically in constrictive pericarditis and that the pattern of right ventricular hypertrophy regresses after pericardiectomy must imply another mechanism

Mounsey[4] noted that the areas of the exterior of the surface of the heart overlying the four valve rings are those at which the greatest movement takes place during the cardiac cycle In the normal heart movement of visceral upon the parietal layers of the pericardium might be expected to be greatest in these areas In the presence of pericarditis friction will be greatest here also giving rise to a more intense inflammatory reaction and more fibrosis This observation is in keeping with our experience where the pericardium tends to be irregularly thickened but with a predilection for marked fibrosis at the base of the heart

A tentative explanation for the unexpected ECG findings may thus be that in these cases heavy basal fibrosis (short of annular constriction) leads to cardiac distortion and rotation with an alteration of direction of the electrical forces producing a pattern simulating right ventricular hypertrophy

Summary

The ECG changes in 122 cases of constrictive pericarditis have been reviewed Ninety five per cent of tracings were typical and showed a normal QRS axis low voltage and generalized T wave flattening or inversion The remaining six tracings showed evidence of right ventricular hypertrophy and half of these showed right axis deviation in addition In only one could these findings be readily accounted for by the presence of severe fibrotic annular subpulmonic constriction, the remainder are unexplained and it is postulated that cardiac rotation and distortion is causative since none of the other mechanisms of right axis deviation or right ventricular hypertrophy were operative

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The effect of vitamin E on platelet aggregation

Joseph A C Gomes MD
D Venkatachalapathy MD
Jacob I Haft MD FACC
Bronx and New York N Y

Since the optimistic reports by Shute and associates in Canada there has been great interest in vitamin E as a cure or preventative for all forms of heart disease especially that due to coronary artery disease Vitamin E has also been used in the treatment of peripheral vascular disease and intermittent claudication with conflicting results In experimental models thrombosis was discovered in fetal rats dying in mothers which were vitamin E deficient Similarly hyaline thrombi in capillaries in and about the cerebellum were believed to be the primary lesions in the encephalomalacia produced in chicks by a diet deficient in vitamin E

In 1964 Ochaner claimed that tocopherol was of preventive value in thromboembolism because of antithrombin properties Since platelet aggregation is intricately related to thrombosis and since platelet aggregation occurs during the earliest stages of experimentally induced thrombosis it seems probable that agents that prevent platelets sticking to each other and to the vessel wall will be more effective in preventing thrombosis than agents that prevent fibrin formation Renaud and associates in 1970 showed that an increased ratio of saturated plus monounsaturated to polyunsaturated (S + M/P) fatty acids in the platelets of patients with coronary artery disease and the platelets of rats fed a thrombogenic diet correlated with an increased propensity of platelets to aggregate in vitro The antioxidant properties of tocopherol by which it protects the polyunsaturated fatty acids from peroxidation are widely acknowledged by most investigators Hence α tocopherol could conceivably decrease the S + M/P ratio in biologic systems by preventing the peroxidation of PUFA Hypothetically then α tocopherol would bring about an increased availability of PUFA in plasma with increased binding of PUFA by the platelet or this reaction could occur de novo in the platelets leading to a decrease in the S + M/P ratio in the platelets The decrease in the S + M/P ratio in the platelets would in turn lead to a decreased propensity of platelets to aggregate In view of this postulate and for the reasons mentioned the effect of α tocopherol acetate (vitamin E) on platelet aggregation not previously reported was determined

Materials and methods

Platelet aggregation studies were done in 10 men 40 to 60 years of age Group I consisted of five patients with coronary artery disease documented by coronary angiography (three patients) or by a history of a past myocardial infarction (with diagnostic electrocardiographic [ECG] changes) that had occurred at least 6 months prior to the time of study (two patients) All five patients had angina pectoris on moderate exertion with four to six episodes per week requiring four to six tablets of nitroglycerine per week None of the patients had congestive heart failure and none was taking any other medications Group II consisted of five control patients with nonspecific chest pain atypical for angina and no ECG findings negative exercise tests no demonstrable coronary artery disease by angiography

From the Cardiology Section of the Bronx VA Hospital and the Mount Sinai School of Medicine, New York N Y

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Reprint requests Dr Jacob I Haft MD FACC Chief Cardiology Department, St. Michaels Medical Center 306 High St Newark N J 07102.

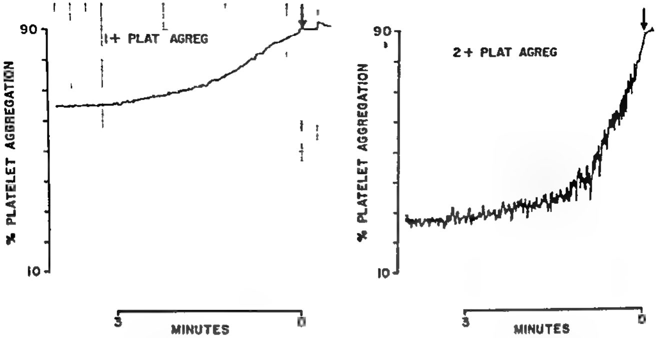

Fig 1 Grading of platelet aggregation response curves Left panel shows 1+ platelet aggregation (partial aggregation first phase only) Right panel 2+ platelet aggregation (irreversible aggregation response)

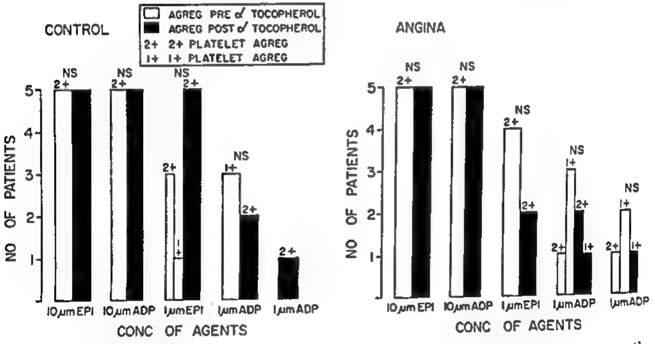

Fig 2 Bar graphs comparing pre-α tocopherol and post-α tocopherol platelet aggregation response curves in the control and angina groups

(two patients) and no relief of chest pain with nitroglycerine

Platelet aggregation studies were performed by the optical density method of Born [12] as modified by Mustard and associates [13] Venous blood was collected in siliconized tubes by a double syringe method Nine volumes of blood were added to one volume of 3 8 per cent sodium citrate Samples were centrifuged at 1,000 r p m for 10 minutes at room temperature and the platelet rich plasma (PRP) was removed The platelet count of the PRP was 250 000 to 300,000 per cubic millimeter The remaining blood was centrifuged at 2 500 r p m for 20 minutes to obtain platelet poor plasma (PPP) The PRP was placed in a cuvette of a chrono log aggregometer and stirred at 1 200 r p m at 37° C Dose response curves were recorded on a moving strip chart recorder and were induced by adding to PRP adenosine diphosphate (ADP, Sigma Company St Louis Mo) to

achieve final concentrations of 10 1 and 0 1 μM and epinephrine (adrenaline chloride Park Davis Company Detroit Mich) to achieve concentrations of 10 and 1 μM The per cent transmission of PRP was set at 90 and that of PPP at 10 Aggregation studies were done in a fasting state prior to tocopherol acetate (vitamin E) and after 1 000 I U of tocopherol acetate (vitamin E) per day for 8 days Serum triglycerides and cholesterol were measured before and after tocopherol administration

Aggregation was graded as 1+ (partial aggregation first phase only) and 2+ (irreversible aggregation or biphasic response) as shown in Fig 1 Pre tocopherol aggregation response curves were compared with post tocopherol aggregation curves with the patients serving as their own controls

Results

Prior to tocopherol there was no significant difference in the incidence of 1+ or 2+ aggregation response to the various concentrations of ADP or epinephrine between the control and angina groups Similarly after tocopherol no significant difference was found in either group when compared with pre tocopherol aggregation response curves (Fig 2) When all 10 patients were compared before and after tocopherol no significant changes were observed (Fig 3) Similarly no trends were observed after tocopherol in either direction (i e increased or decreased aggregation responses) in all 10 patients (Fig 4) Serum cholesterol and triglycerides were normal in all 10 patients namely 210 ± 20 and 140 ± 20 mg per 100 ml and did not significantly vary after tocopherol All patients felt a sense of well being and no deleterious effects were observed in either the treated or the nontreated group No significant difference in the frequency of anginal episodes was noted

Discussion

In the 1940 s Shute and his colleagues described marked improvement in an unselected series of 84 consecutive patients with angina pectoris However controlled studies carried out by Donegan and associates [7] Ravin and Katz [15] and Makinson and associates [8] showed no beneficial effects Boyd and associates[2] and Livingston and Jones[3] reported improvement in patients with peripheral vascular disease and intermittent claudication however Hamilton and associates reported no significant beneficial effect Williams and associates[4] in a more recent study reported improvement in two thirds of 30 patients with femeropopliteal occlusion and poor distal arteries after taking 400 mg of tocopherol four times a day for 3 months as tested on an electric treadmill Zierler and associates[17] and Kay and associates reported that tocopherol phosphate increased plasma antithrombin activity Maracci and Comera [9] found that tocopherol phosphate had a strong antithrombin activity whereas tocopherol acetate had none Similarly Monkhouse[20] found that the antithrombin effect of tocopherol phosphate in vitro was due to the phosphate ion and not to tocopherol per se Kiffer and Olson [21] in their unpublished results found no antithrombin effect of tocopherol claimed by Ochsner [9]

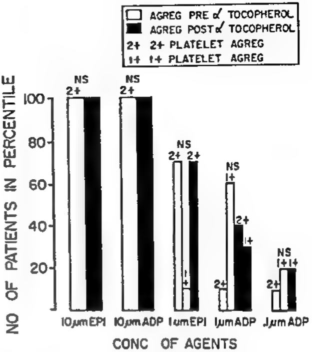

Fig 3 Bar graphs comparing pre-α tocopherol and post-α tocopherol platelet aggregation responses to various concentration of aggregating agents in all ten patients expressed in percentile

Recently Korsan Bengtsen and associates[2] found in a group of postmyocardial infarction patients who were given α tocopherol 300 mg per day a highly significant prolongation of the plasma clotting time after 18 44 and 64 weeks of treatment They found no change in the platelet count nor any change in platelet adhesiveness To

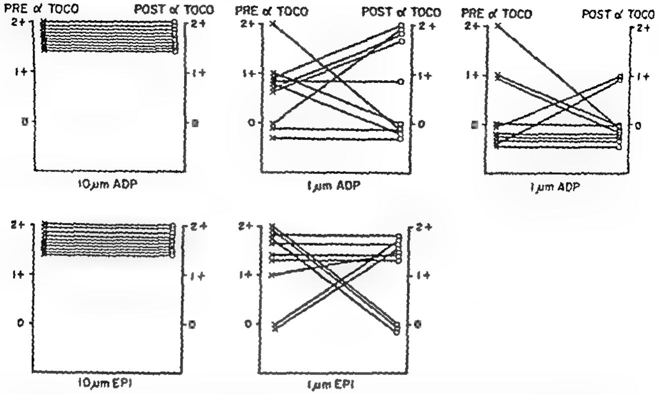

Fig 4 Linear graphs comparing pre and post-α tocopherol aggregation responses to various concentration of aggregating agents With 10μm of ADP and 10μm of epinephrine there is no change pre and post-α tocopherol With 1μm of ADP 0 1μm of ADP and 1μm of epinephrine some show more aggregation others less and some no change No significant trends are observed in either direction

explain the observation of a prolonged clotting time they postulated that a higher amount of highly unsaturated fatty acids was incorporated in the phospholipid fraction of the platelets together with α tocopherol leading to a change in the quality of the platelet membrane thereby causing a reduced release of platelet factor 3 Interestingly they found no change in platelet adhesiveness and they did not study the effect on platelet aggregation

If our hypothesis that α tocopherol might decrease the S + M/P ratio in the platelets were valid, we would expect that α tocopherol would decrease the ability of platelets to aggregate This did not occur It is possible that this effect might have occurred after a prolonged course of therapy and that 8 days was an insufficient time to result in a change of platelet activity but this is unlikely There was no significant change in platelet function with α tocopherol [1] Previous studies have shown that α tocopherol levels go up significantly in the plasma and RBC reaching a peak at 10 hours [24] Cross incubation experiments with plasma and RBC s have shown that α tocopherol diffuses easily from plasma to RBC s and vice versa [24] and although there are no data on turnover and levels of α tocopherol in the platelets as yet it is likely that vitamin E would enter platelets rapidly In addition, because of the natural life span of platelets 8 days of therapy should be sufficient to effect the generation of platelets tested even if the α tocopherol entered the platelet only as it developed Furthermore most drugs that affect platelet function do so within a short time period after administration It has also been shown that platelets may escape the antiaggregating effect of a drug (e g Atromid) [5] when it is given for a prolonged period of time

The question whether tocopherol is effective in the prevention or treatment of thromboembolism is still open and can be solved only by large trials It seems however, that if vitamin E exerts any beneficial effect in the prevention or treatment of thromboembolic phenomena coronary artery disease peripheral vascular disease, or the initiation of athrogenesis it does not do so via an effect on platelet aggregation

Summary

Platelet aggregation studies were performed in five men with coronary artery disease and angina pectoris and five men with nonspecific chest pain before and after receiving 1 000 I U of α tocopherol acetate orally per day for 8 days

There was no significant difference in the platelet aggregation response to three concentrations of ADP and two concentrations of epinephrine between the pre and post-vitamin E periods among the 10 patients If tocopherol acetate (vitamin E) has any beneficial effect on the prevention of thromboembolism or in the treatment of angina pectoris and peripheral vascular disease it is not via inhibition of platelet aggregation

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A controlled trial of intramuscular lidocaine in the prevention of premature ventricular contractions associated with acute myocardial infarction

Jang B Singh, M D F R C P (C)
Stanley L Kocot, M D
Worcester Mass

Intravenous lidocaine has become an established form of therapy in coronary care units for the prevention of premature ventricular contractions (PVC s) It has been necessary to follow the bolus injection of intravenous lidocaine by an intravenous infusion to maintain a blood level adequate for arrhythmia prevention The mortality rate from myocardial infarction is highest in its early phase 25 to 30 per cent of deaths occur in the first hour and 60 per cent of the patients dying from manifestations of coronary artery disease never see the emergency room of a hospital or a physician[1, 2] The major cause of death in the prehospital phases of acute myocardial infarction has been attributed to major arrhythmias The significance of this problem is quite clear when one notices that the number of patients dying suddenly is 400 000 per year or approximately 1,000 per day

No matter how demonstrably effective lidocaine is in abolishing the PVC s that so often trigger lethal ventricular arrhythmias the luxury of intravenous administration is not always convenient or feasible in emergency situations Previous studies have shown that intramuscular administration of lidocaine may produce therapeutic blood levels of the drug within 10 to 15 minutes after the administration of the drug[3, 5] The objective of this trial was to study the effects of intramuscular lidocaine in a double blind placebo controlled study on (1) occurrence of ventricular arrhythmias, (2) changes in blood pressure heart rate and selected laboratory examinations and (3) occurrence of any adverse effects

Subjects and methods

Fifty four patients admitted to the coronary care unit of the St Vincent Hospital were included in this double blind placebo controlled study Twenty seven patients received 4 5 mg per kilogram of lidocaine hydrochloride* as a 10 per cent solution in the deltoid muscle Only patients with electrocardiographic (ECG) changes of acute myocardial infarction and symptoms of less than 18 hours duration were admitted to the trial To permit comparison of the development of PVC s patients with five or more PVC s per minute in the control period or those with no control data were excluded from the study Patients with congestive heart failure hypotension, shock serious cardiac arrhythmias or a heart rate less than 50 per minute were excluded Recent use of any antiarrhythmic agent excluded patients from this study This was defined as the use of lidocaine less than 4 hours prior to injection, procainamide quinidine, or propranolol less than 12 hours and diphenylhydantoin less than 24 hours The two groups were well matched with respect to sex age weight duration of symptoms prior to the study, and concurrent medications (Table I)

Blood pressure was measured by sphygmoma

From St Vincent Hospital and University of Massachusetts School of Medicine Worcester Mass

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Reprint requests Jang B Singh M D Director Cardiac Catheterization Unit 25 Winthrop St Worcester Mass 01610

*Xylocaine supplied by Astra Pharmaceutical Worcester Mass

Table I Intramuscular lidocaine patient characteristics

	Lidocaine	*Placebo*
Males	21	20
Females	6	7
Total	27	27
Mean age (yr)	54.2 ± 1.6	57.8 ± 2.0
Mean weight (kg)	83 ± 3.0	81 ± 2.1
Acute myocardial infarction		
Anterior	14	14
Posterior	13	13
Congestive heart failure	1	0
Mean time (hr) *(onset of symptoms to injection)*	4.0 ± 0.57	5.16 ± 0.66

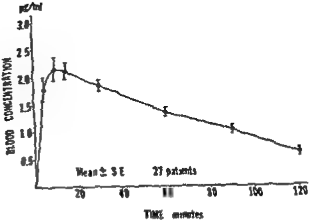

Fig 1 Blood concentrations of lidocaine after intramuscular injection of 4.5 mg per kilogram of lidocaine HCl into the deltoid muscle

nometer before the injection and then 5 10 30 60 90 120 180 and 240 minutes after the initiation of the study Heart rate and rhythm were observed by continuous oscilloscope monitoring recorded on a tape in 25 patients In addition rhythm strips of approximately 2 minutes duration were obtained at the same time as blood pressures were obtained Venous blood specimens for the measurement of lidocaine concentration were obtained prior to and 5 10 15 30 90 and 120 minutes after the injection Lidocaine concentrations were measured by gas chromatography after the method described by Keenaghan and expressed as micrograms of lidocaine base per milliliter of whole blood Rhythm strips were analyzed by one observer without knowledge of the patient's medication and the PVCs were expressed as PVCs per minute Magnetic tape recordings from 25 patients were analyzed by a computer* and PVCs reported for 10 minute intervals A complete count of blood blood urea nitrogen serum glutamic oxaloacetic transaminase creatine phosphokinase serum electrolytes and urinalysis were obtained prior to and 24 hours after the injection

Statistics

Arithmetic means were calculated where appropriate and all estimates of variability were expressed as standard errors of the mean (S E) Three dimensional analysis of variance (subject × dose × time) was employed to compare effects of treatment on heart rate and blood pressures A chi square test was used to compare the two treatment groups for comparability of the following variables sex anatomic location of infarction and presence of congestive heart failure Student's t test was used to compare differences in the treatment groups with respect to age weight and duration of symptoms prior to injection and to compare differences in laboratory values obtained before and after the injections

Results

Fifty four patients were treated 27 receiving the placebo and 27 receiving the active drug Four patients were excluded from the lidocaine group two because of lack of control data one patient had serious ventricular arrhythmias soon after the initiation of the study and another developed nodal rhythm with aberrancy 60 minutes after the intramuscular injection of lidocaine One patient was excluded from the placebo group because of lack of control data Patient characteristics are tabulated in Table I There were 14 patients in each group with anterior myocardial infarction and 13 with posterior or inferior myocardial infarction Only one patient in the lidocaine group had mild congestive heart failure and one patient in the placebo group had hypokalemia The two groups are well matched in other aspects

Blood levels of lidocaine and standard error are plotted against time in Fig 1 No lidocaine was reported in any preinjection specimen in either group Five minutes after the injection the mean

*PDP 11 high-speed version (Digital Equipment)

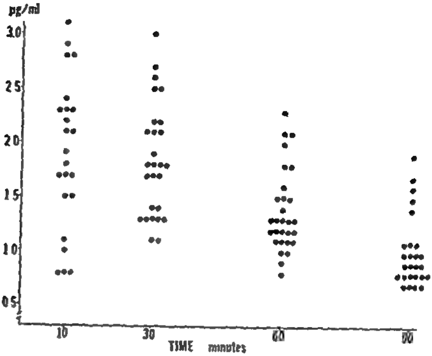

Fig 2 Blood concentrations of lidocaine after intramuscular injection (Lidocaine 4.5 mg per kilogram)

Table II Incidence of patients developing PVC s after injection of placebo or lidocaine (number of patients developing PVC s/number of patients treated)

Minutes after injection	*Placebo*	*Lidocaine*
Control	2/26	4/23
15	8/26	0/23
30	9/26	0/23*
60	11/26	0/23
90	11/26	2/23
120	13/26	3/23
180	15/26	5/23

*$p < 0.05$

blood concentration of lidocaine was 1.81 ± 0.22 µg per milliliter and 10 minutes after the injection it reached a peak concentration of 2.18 ± 0.22 µg per milliliter Thereafter, the blood concentration declined slowly to 1.37 ± 0.07 µg per milliliter at 60 minutes, 1.03 ± 0.06 µg per milliliter at 90 minutes after injection, and 0.81 ± 0.05 µg per milliliter 120 minutes after the injection of 4.5 mg per kilogram of lidocaine hydrochloride as a 10 per cent solution Individual peaks ranged from 1.3 to 5.8 µg per milliliter Only one patient reached levels above 5 µg per milliliter (Fig 2) These blood levels compared favorably with the previously reported studies[5,7,8]

Two patients in the placebo group and four of the 23 patients in the lidocaine group had PVC s in the control period Table II shows the cumulative number of patients developing PVC s after the initiation of the study Nine of the 26 patients in the placebo group developed PVC s during the first 30 minutes compared to none of the 23 patients in the lidocaine treated group ($p < 0.01$) Up to 60 minutes after the injection no patients in the lidocaine group had developed PVC s whereas two additional patients in the placebo group had developed PVC s It was only at 90 minutes after the injection that two patients in the lidocaine group showed any evidence of ventricular irritability The highly significant difference between groups continued up to 180 minutes of observation at which point 15 of the 26 patients in the placebo group compared to only 5 of the 23 patients in the lidocaine group had shown PVC s These data are presented as a cumulative percentage of patients developing PVC s after the initiation of the study plotted against time in Fig 3 Computer analysis of continuous magnetic tapes in 25 patients revealed (Fig 4) that six of the 15 patients in the placebo group and three of the 10 patients in the lidocaine group had PVC s during the control period Fig 4 reveals the cumulative number of patients developing PVC s in each group plotted against time The results are somewhat similar to those derived from the analysis of the 2 minute rhythm strips except

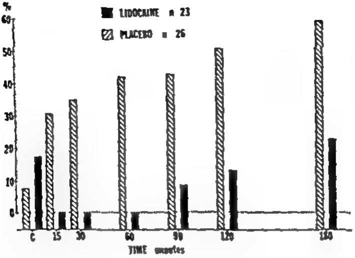

Fig 3 Percentage of patients with premature ventricular contractions.

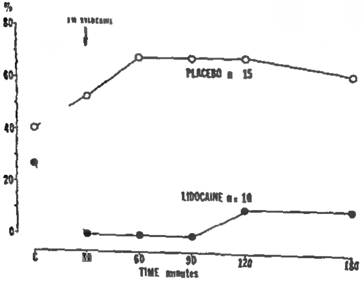

Fig 4 Percentage of patients with PVC s (data taken from magnetic tapes)

that the total number of patients developing PVC s in the placebo group in the first 90 minutes is 66 per cent as compared to only 43 per cent observed with rhythm strips The effect of systolic blood pressure was 138 7 ± 3 7 mm Hg prior to placebo injection After placebo the blood pressure declined to a minimum of 122 0 ± 3 2 mm Hg at 240 minutes The mean systolic pressure in the lidocaine group was 147 4 ± 7 1 mm Hg during the control period which gradually declined to 138 5 ± 5 6 mm Hg at 180 minutes One patient receiving lidocaine developed a systolic blood pressure of less than 90 mm Hg 2 hours after the injection and sinus bradycardia 1 hour after injection This patient had idionodal rhythm and these changes coincided with the change of rhythm Three patients receiving placebo developed blood pressures of 90 mm Hg or less 15 90 and 120 minutes respectively after injection Heart rates are shown in the upper half of Fig 5 An analysis of variance failed to detect statistically significant effects due to time dose or time dose interaction One additional patient receiving lidocaine developed bradycardia (heart rate 50 beats per minute) [illegible] minutes after the injection which persisted throughout the period

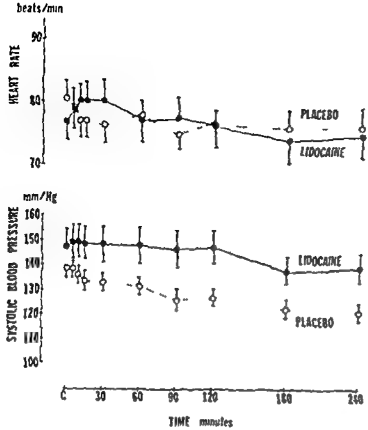

Fig 5 Effect of intramuscular lidocaine and placebo on systolic blood pressure and heart rate

of study No patient in the placebo group had comparable bradycardia One patient in the lidocaine group became anxious and confused approximately 10 minutes after injection One patient receiving placebo injection complained of weakness and warmth approximately 15 minutes after the injection There were no consistent changes in group means of blood pressure heart rate or chemical laboratory examinations which appeared to be an adverse effect

Discussion

In the early phases of acute myocardial infarction premature ventricular contractions are the forerunners of potentially lethal arrhythmias The prevalence of PVC s varies with the location and severity of the infarct presence of congestive heart failure and the age and sex of the patient [1] In our study, although the high risk patients were excluded by the requirements of the protocol even then the incidence of PVC s in the placebo group was 66 per cent within the first 2 hours after the initiation of the study The two groups have been well matched selection of patients has been unbiased and the PVC s have been scanned either on rhythm strips or with a computer programmed to pick up abnormal beats depending upon the QRS width and in doubtful cases have been confirmed on rhythm strips also The dosage of lidocaine hydrochloride used has been based on body weight (4 5 mg per kilogram) and in dosages which have been previously shown to produce therapeutic levels A lidocaine blood level of 1 to 1 2 μg per milliliter has been considered as the lowest effective concentration for abolition of ventricular arrhythmias [10, 11] In our study the therapeutic levels were obtained within 5 minutes and peak levels at 15 minutes The drug was still available in low therapeutic levels even at 90 minutes after the injection The site of injection has been shown to affect the plasma concentration levels and the deltoid muscle appears to be the site of choice for most optimal blood levels Cohen and associates[5] reported lower blood levels with 10 per cent solution and attributed this to the solubility characteristics of the drug at tissue pH hypertonicity of the solution and small volume of the injectate We did not experience this problem in our group of cases Therefore 10 per cent lidocaine may be the preferred concentration of the drug to use since the injection required in most cases would be more reasonable in volume

Previous reports have shown intramuscularly administered lidocaine to be effective in suppressing PVC s in acute myocardial infarction [3, 8, 11] but none of these studies was controlled In the present placebo controlled study the difference in the cumulative incidence of patients with PVC s in the placebo group as compared to the lidocaine group becomes quite clear even at the 15 minute level where 32 per cent of the placebo group had shown some ventricular irritability compared to none in the treatment group (Fig 3) This is even more marked in the smaller group of patients where the magnetic tape was subjected to computer analysis

Of the 15 cases in the placebo group where the tapes were analyzed for morphology of PVC s six cases were demonstrated to have coupled (two in a row) and multifocal PVC s No comment can be made about the morphology of PVC s in the treated group as this study was designed to be prophylactic It can only be assumed that if not treated they would have developed arrhythmias similar to the control group The analysis of rhythm strips as done in some previous studies and in part in this study only underestimates the incidence of arrhythmias The separation of two

groups of patients continues up to 180 minutes however no definitive conclusions can be drawn beyond a 90 minute point where blood levels of the lidocaine base in whole blood start going below the effective therapeutic levels (Fig 1)

Intramuscular lidocaine (4 5 mg per kilogram) did not produce blood levels in the toxic range The serum concentration of lidocaine above 5 μg per milliliter may have a depressant effect on the left ventricular function[5] Previous studies have shown no significant changes in hemodynamic indices in patients receiving intramuscular lidocaine[3, 4] Mogensen[5] observed no significant changes in heart rate in 42 patients with idioventricular rhythm receiving intravenous lidocaine infusion Any significant effect on the A V conduction producing clinical implications because of lidocaine administration in therapeutic levels is doubtful[6] No significant changes in heart rate or blood pressures were observed in either group in this study One patient who did develop bradycardia after lidocaine injection had entered the study with a rate of 58 per minute and continued to have a rate of 60 per minute even with a lidocaine blood concentration less than 1 μg per milliliter

From this study it can be concluded that intramuscular lidocaine in the dose of 4 5 mg per kilogram of body weight produces rapid effective blood levels in patients with acute myocardial infarction Lidocaine effectively suppresses PVC's in the early phases of acute myocardial infarction and can be safely administered without any major side effects

Major efforts in the coronary care units toward prevention of arrhythmias have resulted in significant improvement in mortality statistics in acute myocardial infarction The mechanism of sudden death in the ambulatory patient with coronary heart disease and the hospitalized patient with acute myocardial infarction may be similar[11] There is always a considerable delay from the time of onset of symptoms and availability of suitable medical aid to the patient Prophylactic administration of intramuscular lidocaine either self administered or by a paramedical person to high risk patients may reduce the incidence of early deaths in acute myocardial infarction

Summary

Intramuscular lidocaine administration is known to produce blood concentration levels considered to be therapeutic for prevention of premature ventricular contractions This double blind study was designed to study the effect of intramuscular lidocaine in the prevention of PVC's in acute myocardial infarction Forty six patients with confirmed acute myocardial infarction without congestive heart failure shock or major arrhythmias were admitted to the trial Twenty one patients received 4 5 mg per kilogram of intramuscular lidocaine and 25 patients received placebo in the deltoid muscle within 14 hours of the onset of symptoms Rhythm strips of 2 minutes duration blood pressure heart rate and blood specimens for blood concentration levels were obtained prior to and 5 10 15 30 60 90 and 120 minutes after injection The mean blood concentration level of lidocaine was 1 81 ± 0 22 μg per milliliter at 5 minutes reached a maximum of 2 18 ± 0 22 μg per milliliter at 10 minutes and was still 0 81 ± 0 05 at 120 minutes Analysis of rhythm strips revealed that only three of 21 patients (14 per cent) in the intramuscular lidocaine group developed at least one PVC as compared to 13 of 25 (52 per cent) in the placebo group ($p < 0\ 0005$) No significant toxic effects were noted This study suggests that intramuscular lidocaine may significantly reduce potentially fatal arrhythmias in early phases of acute myocardial infarction

The authors are grateful to the Astra Pharmaceutical Co., Worcester Mass Dr M B Meyer Mr Paul Kamp and Mr Ben Duce for their assistance and cooperation Appreciation is also entered to Ms Lucille Soter and Ms Patricia Garcia for their help in this study

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The localization of coronary artery stenoses by 12 lead ECG response to graded exercise test

Support for intercoronary steal

Duncan Robertson M B BS F R C P (C) M R C P (U K)
William J Kostuk M D F R C P (C)
Suraj P Ahuja M B BS F R C P (C) F A C P
London Ontario Canada

There is general agreement that the incidence and degree of postexercise ST segment depression in the electrocardiogram (ECG) correlates directly with the number of significantly diseased coronary arteries. False negative ECG stress tests may be frequently accounted for by inadequate exercise stress conveniently measured by the patient's heart rate response or by minor and hemodynamically insignificant lesions in the coronary arteries. Other possible causes for a false negative stress test may be (1) failure to use 12 ECG leads after exercise since the ischemic ST segment change could occur in leads not recorded and (2) good collateral flow to the territories supplied by a severely stenosed vessel. Some authors have concluded that there is no correlation between the presence of collaterals and ECG changes ventricular dysfunction or physical work capacity.

The availability of an ECG system which permits the rapid recording of a 12 lead ECG following exercise has permitted us to correlate the localization of coronary artery stenoses and the presence of intercoronary collaterals with the localization of ischemic change on the 12 lead ECG.

The data of all patients who had been subjected to graded exercise testing and cardiac catheterization in our laboratory in the period from March 1973 to December 1974 were reviewed. Thirty nine patients were found to have unequivocally abnormal exercise stress tests and abnormal coronary arteriograms. Three patients were excluded from the total group because of coexisting valvular heart disease; however no patient with coronary artery disease alone was excluded.

Method

Graded exercise testing was performed as part of cardiologic evaluation of patients suspected of having ischemic heart disease. The patients were exercised on a Quintron treadmill with elevation of the speed and incline at 3 minute intervals. Exercise was continued until (1) the patient's pulse rate reached 90 per cent of the predicted maximal heart rate, (2) fatigue, chest pain or dyspnea necessitated discontinuing the test, or (3) ischemic ST changes or frequent PVC's occurred. A physician was in attendance at all times and a DC defibrillator and resuscitation equipment were at hand. A 12 lead ECG was recorded before exercise, immediately after exercise, and at 2, 4, 6, 8 and 10 minutes after exercise. The ECG leads were recorded by a semiautomatic system (Marquette) that permitted simultaneous inscription of three leads at a time each of 2.5 seconds duration. Sets of simultaneous leads were I, II, III; aV_L, aV_R, aV_F; V_1 to V_3; and V_4 to V_6.

Continuous oscilloscopic display of Leads V to V_6 was observed during exercise and at the termination of each level of exercise an ECG recording of these leads was made. Before and after exercise the blood pressure was recorded and the heart auscultated. The ECG equipment used

From the Cardiac Investigation Unit, University Hospital, London, Ontario, Canada.

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Reprint requests: Dr S P Ahuja, Cardiac Investigation Unit, University Hospital, 339 Windermere Rd, London, Ontario, Canada.

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17 Koch W J Antiarrhythmic prophylaxis in ambulatory patients with coronary heart disease Arch Intern Med 129 763 1972

Prev. infarct	*Coronary arteriogram†* R	*LM*	*LAD*	*CX*	*Collaterals*	*Ventriculogram‡*
	1	1	4	1	RT→LAD	1
Inf	2	2	4	3	LAD→RT	2
Inf	3	0	4	1	RT→LAD CX→RT	2
Ant	1	0	3	0		2
	1	2	3	2		1
	1	0	3	0	Bypass to LAD	1
Inf	3	0	3	0		
	0	0	3	1		1
	1	2	1	2		2
	1	2	2	0		0
	1	0	0	3		0
Inf	4	0	0	3	CX→RT RT→CX	2
Inf	4	0	1	4	LAD→RT	2
Inf	4	0	1	4	LAD→RT	2
Ant	4	0	3	3	RT→LAD	2
Inf	2	0	3	3		0

well as the presence and size of collateral vessels.

The ECG changes were considered concordant when (1) ischemic ST segment developed in Leads II, III, and aV_F after exercise in patients with greater than 90 per cent obstruction of the right coronary artery or (2) ischemic changes occurred in Leads I, aV_L, and/or the chest leads in patients with greater than 90 per cent obstruction of the divisions of the left coronary artery or greater than 50 per cent obstruction of its main stem.

Results

The results of the graded exercise stress test, coronary arteriogram, and left ventriculogram of 32 patients are given in Table I. Groups 1A, 1B, 1C, and 1D (total 16 patients) include patients with left coronary artery disease with or without inferior myocardial infarction. Eight of these patients had greater than 50 per cent stenosis of the right coronary artery and of these six patients had greater than 90 per cent stenosis. All of the eight patients had ECG evidence of previous inferior wall myocardial infarction and seven of the eight patients showed diaphragmatic akinesis or dyskinesis on the left ventriculogram. With one exception (patient R. A. H.) the ST segment changes were confined to Leads I, aV_L, and V_2 through V_6. Comparison of Group 1A (primarily left anterior descending coronary artery disease) with Group 1C (primarily left circumflex coronary artery disease) shows no difference in the localization of ST segment change. The heart rate achieved by this group during exercise stress testing was 80 per cent of the predicted maximal. (Mean achieved heart rate 139, mean 90 per cent of the predicted maximal heart rate 174.)

Group 2 (Table II) includes only three patients who have severe stenosis of both the right and left coronary arteries. (Patient H. G. is included as severe coronary artery stenosis because of a lesion of between 50 and 90 per cent stenosis in the left main coronary artery in addition to a similar lesion in the left anterior descending.) In all three patients in Group 2 ST changes were observed in the inferior leads (II, III, and aV_F) in addition to the precordial leads. The heart rate achieved by this group during exercise stress testing was 77 per cent of the 90 per cent predicted maximal. (Mean achieved 133, mean 90 per cent—predicted maximal 172.)

Group 3 (Table II) included two patients with primarily right coronary artery disease. In these patients either the left coronary artery was free of stenoses or only minor lesions (less than 50 per cent) were observed. In both these patients ST segment changes were restricted to Leads II, III, and aV_F.

Groups 4A and 4B (Table III) include a total of 11 patients in whom at first sight the ECG ST segment changes do not appear to be concordant with the coronary artery stenoses. In Group 4A, however, severe stenosis or occlusion is present in one coronary artery (in two cases the left anterior descending and in two cases the right coronary artery). In all four cases the other major coronary vessel was not severely diseased and supplied large collateral branches to the distal part of the stenosed or occluded coronary artery.

In Group 4B, more severe grades of stenoses (between 50 and 90 per cent) are present in the vessels supplying the collaterals. The heart rate achieved by this group in exercise stress testing

Table I Groups 1A to 1D*

				Treadmill exercise stress test																	
				Heart rate/min		ST segment changes															
Group	Patient	Age (yr)	Sex	90% max predicted	Achieved	I	II	III	AV_R	AV_L	AV_F	V_1	V_2	V_3	V_4	V_5	V
1A	F E M	47	M	177	110										Y	\	
	W C H	64	M	165	130	\							\	Y	Y	Y	\
	D W C	47	M	170	160												\
	G P	46	M	177	125								\	Y	\		
	R A H	64	M	165	140		\									λ	\
	J J C	57	M	170	131										\	\	Y
	W V R	45	M	179	130										\		
	R T	48	M	179	119										Y	\	\
1B	B E B	39	M	186	175										Y	Y	Y
	W H M	45	M	179	158											Y	Y
1C	J W R	55	M	171	130								Y	\	Y	Y	
	G K M	42	M	180	162									\	\	\	\
	F H	58	M	169	112								λ	\	\	\	\
	J P B	47	M	177	120								\	\	X	\	\
1D	J L	45	M	179	165	\					λ		\	\			
	E W	69	M	161	130	\							\	Y	\	\	\

Group 1 patients with left coronary disease with or without concomitant inferior myocardial infarction 1A LAD disease 1B left main coronary artery disease 1C primarily left circumflex coronary artery disease 1D major obstruction to left anterior descending and circumflex In all four groups, if significant right coronary artery disease is present then previous inferior infarction with akinesis or dyskinesis
†R right coronary artery LM left main stem coronary artery LAD left anterior descending artery including diagonal branch CX left circumflex including marginal branch Grading of coronary arteriogram 0 = normal 1 = < 50% stenosis 2 = > 50% < 90% stenosis 3 = > 90% < 100% stenosis 4 = occlusion
‡Pr prolapsing mitral valve Grading of ventriculogram 0 = normal 1 = hypokinesis 2 = akinesis or dyskinesis

exceeded the standard set by the American Heart Association Committee on electrocardiography The ECG electrodes were attached before the resting tracing was obtained and remained in place throughout the study With this system a 12 lead ECG could be obtained in 10 seconds Each tracing was examined without reference to the coronary arteriogram The leads in which unequivocal ST segment changes occurred were recorded Positive responses were those in which downsloping or horizontal ST segment depression of greater than 1 mm, lasting for longer than 0 08 second, or "ischemic type" ST segment elevation occurred

Cardiac catheterization was performed by the percutaneous Seldinger technique from the right groin Left ventricular cineangiography was accomplished in the 30 degree right anterior oblique and in the 45 degree left anterior oblique positions Selective coronary arteriography was performed with Judkin's preformed catheters Multiple injections of the right and left coronary arteries were performed in the 30 degree right anterior oblique, 15 degree right anterior oblique and 45 degree left anterior oblique positions In some circumstances injections were made in the anteroposterior plane The coronary arteriogram and left ventricular cineangiogram were recorded on 35 mm cinefilm at 60 frames per second

The results of coronary arteriograms and ventriculography were reviewed by at least two of the authors (D R and E P A or D R and W J K) In each case the coronary arteriogram was reviewed without reference to the exercise stress test, and a consensus obtained as to the localization and severity of coronary stenosis as

Prev infarct	Coronary arteriogram R	LM	LAD	CY	Collaterals	Ventriculogram
	4	1	3	0	CY→RT	1 Pr
	4	[illegible]	3	1	CY→RT	2
Inf	3	2	2	1		1
	4	0	0	0	CX & LAD→RT	1
	4	0	1	1	LAD→RT	0 Pr

Prev infarct	Coronary arteriogram R	LM	LAD	CX	Collaterals	Ventriculogram
Ant	1	1	4	1	RT→LAD	1
	1	0	4	1	RT→LAD	2
Inf	3	1	1	1	LAD→RT	[illegible]
	4	[illegible]	0	0	LAD→RT	1
	4	[illegible]	2	1	LAD→RT	0
Inf	4	0	2	[illegible]	LAD→RT	1
Inf	3	[illegible]	2	1	LAD→RT	2
Inf	1	0	3	3	RT→LAD	0 Pr
Ant	[illegible]	3	[illegible]	[illegible]	RT→LAD	1
	4	[illegible]	2	1	LAD→RT	0 Pr
	2	1	4	4	RT→LAD RT→CX	[illegible]

coronary arteries without old infarction and with ECG changes only in the anterior chest leads The heart rate response in this patient was 74 per cent of predicted maximum compared with a mean of [illegible] per cent of predicted maximum for all other patients

Discussion

There is at the present time no standard method of exercising [illegible] patient during exercise stress test nor is there any standardized ECG lead system

Of the three methods of exercise stress testing in common use namely the Master two step test bicycle ergometry and graded exercise stress testing on an elevating treadmill we have chosen the latter method for the following reasons The end point is determined by the patient s heart rate response the exercise being terminated when the patient has achieved 90 per cent or more of his predicted maximal heart rate or upon the development of chest pain fatigue dyspnea or other subjective symptoms which necessitate discontinuing the procedure We recognize two important limitations of this test namely the inability to obtain intraexercise blood pressure recordings and the poor quality of the intraexercise ECG as compared with that obtained during bicycle ergometry

The electrode positioning for ECG recording during exercise has not been standardized[1] and the investigator has a choice of numerous single lead or multiple lead systems Master and associates[6] found that the limb leads more commonly showed ST segment changes than the chest leads and the majority of abnormal changes were in Leads I and II Brady[7] describing an extensive experience with Master s two step test recorded Leads I II V_2 V_4 and V_6 Sheffield recommended the use of V_2 V_5 and aV_F[8] or if a single lead was to be used the use of V_5 or whichever precordial lead had the largest R wave Most of the ischemic ECG changes are seen in the 2 minute postexercise tracing and in most cases the ECG has returned to normal by [illegible] minutes

False negative test results may be due to inadequate exercise stress Lewis and Wilson[10] performed graded exercise tests and double Master s step test on the same patients and found 81 per cent positive with the graded exercise test and 61 per cent positive in the double Master s step test It is possible that with the use of a limited number of leads or single lead ischemic ST segment depression may be missed A negative exercise stress test cannot unequivocally rule out even significant coronary artery disease In correlating postexercise ECG s with pathologic grading of coronary artery disease Mattingly[3] found that in patients with Grade 2/4 coronary artery disease at autopsy only one out of 17 had shown ischemic depression in exercise testing Even in those patients graded 4/4 six out of 16 patients did not show ischemic depression in the postexercise ECG He concluded that ST segment change was present only when severe and diffuse coronary artery disease was present

Table II Groups 2 and 3*

Group	Patient	Age (yr)	Sex	Treadmill exercise stress test: Heart rate/min: Produced	Achieved	ST segment changes: I	II	III	AV_R	AV_L	AV_F	V	V	V	V_4	V_5	V
2	T A S	58	M	169	90		\				\				\		X
	A A M	52	M	173	160		\	\			\					X	\
	R G	51	M	174	149		\	\			\			\	\	\	\
3	D W	47	M	177	150		\	\			\						
	J R	32	M	175	189		X	\			\						

Group 2 major stenoses of left and right coronary arteries Group 3 primarily right coronary artery disease Abbreviations as in Table I

Table III Groups 4A and 4B*

Group	Patient	Age (yr)	Sex	Treadmill exercise stress test: Heart rate/min: 90% max predicted	Achieved	ST segment changes: I	II	III	AV_R	AV_L	AV_F	V	V	V	V	V_5	V_6
4A	F A I	61	M	167	125		X	\			\						
	G N	45	F	179	120		\	\			\						
	J A H	43	M	180	113		X	\			\			\	\	\	\
	D F	49	M	176	145	\	X	\			\		\	\	\	\	\
4B	V D	62	F	167	120									X	\	\	
	J T P	40	M	182	150									\	X	\	\
	H W R	44	M	180	149								\	\	\	\	
	R M	54	M	171	175		X	λ								\	X
	G R L	35	M	186	110		\							\	\		
	M C	60	M	163	92		X								X	X	\
	P J	45	M	179	103	X	\	λ					\	X	X	\	\

Group 4A primarily single coronary artery disease with insignificant (< 50% stenosis) in vessel supplying collateral channel Group 4B severe stenosis (> 90%) in one vessel moderate stenosis (< 90%) in vessel supplying collateral channel (patients G H L and R M included in th[e] group because of possibility that the left circumflex was supplying the inferior wall) Abbreviations as in Table I

was 73 per cent of predicted maximal (mean achieved 127 mean predicted 175)

Group 5 (Table IV) is a miscellaneous group in which the ECG changes and coronary arteriographic findings were nonconcordant In patients E H K W K, and H C R coronary artery stenoses were either less than 50 per cent or between 50 and 90 per cent—mild or moderate obstruction and not expected to produce ST segment change In all three cases there was ventriculographic evidence of mitral valve prolapse In patients E W C and J A K the localization of ST segment change could not be clearly related to the coronary artery stenoses and no collateral vessels were demonstrated radiographically to account for nonconcordant ischemic changes Patient A V showed ischemic changes in the inferior leads and in the lateral chest leads with only moderate disease of the right coronary artery and mild disease of left anterior descending and left circumflex Patient E F had significant lesions in both right and left

Prev Infarct	*Coronary arteriogram* R	LM	LAD	CX	*Collaterals*	*Ventriculogram*
	4	1	3	0	CX→RT	1 Pr
	4	0	3	1	CX→RT	2
Inf	3	2	2	1		1
	4	0	0	0	CX & LAD→RT	1
	4	0	1	1	LAD→RT	0 Pr

Prev infarct	*Coronary arteriogram* R	LM	LAD	CX	*Collaterals*	*Ventriculogram*
Ant	1	1	4	1	RT→LAD	1
	1	0	4	1	RT→LAD	2
Inf	3	1	1	1	LAD→RT	0
	4	0	0	0	LAD→RT	1
	4	0	2	1	LAD→RT	0
Inf	4	0	2	0	LAD→RT	1
Inf	3	0	2	1	LAD→RT	2
Inf	1	0	3	3	RT→LAD	0 Pr
Ant	1	3	2	2	RT→LAD	1
	4	0	2	1	LAD→RT	0 Pr
	2	1	4	4	RT→LAD RT→CX	2

coronary arteries without old infarction and with ECG changes only in the anterior chest leads The heart rate response in this patient was 74 per cent of predicted maximum compared with a mean of 82 per cent of predicted maximum for all other patients

Discussion

There is at the present time no standard method of exercising a patient during exercise stress test nor is there any standardized ECG lead system

Of the three methods of exercise stress testing in common use namely the Master two step test bicycle ergometry and graded exercise stress testing on an elevating treadmill we have chosen the latter method for the following reasons The end point is determined by the patient s heart rate response the exercise being terminated when the patient has achieved 90 per cent or more of his predicted maximal heart rate or upon the development of chest pain fatigue dyspnea or other subjective symptoms which necessitate discontinuing the procedure We recognize two important limitations of this test namely the inability to obtain intraexercise blood pressure recordings and the poor quality of the intraexercise ECG as compared with that obtained during bicycle ergometry

The electrode positioning for ECG recording during exercise has not been standardized[3] and the investigator has a choice of numerous single lead or multiple lead systems Master and associates[4] found that the limb leads more commonly showed ST segment changes than the chest leads and the majority of abnormal changes were in Leads I and II Brady[7] describing an extensive experience with Master s two step test recorded Leads I II V_4 V_5 and V_6 Sheffield recommended the use of V_4 V_5 and aV_F[8] or if a single lead was to be used the use of V_5 or whichever precordial lead had the largest R wave Most of the ischemic ECG changes are seen in the 2 minute postexercise tracing[9] and in most cases the ECG has returned to normal by 8 minutes

False negative test results may be due to inadequate exercise stress Lewis and Wilson[1] performed graded exercise tests and double Master s step test on the same patients and found 81 per cent positive with the graded exercise test and 61 per cent positive in the double Master s step test It is possible that with the use of a limited number of leads or single lead ischemic ST segment depression may be missed A negative exercise stress test cannot unequivocally rule out even significant coronary artery disease In correlating postexercise ECG s with pathologic grading of coronary artery disease Mattingly[2] found that in patients with Grade 2/4 coronary artery disease at autopsy only one out of 17 had shown ischemic depression in exercise testing Even in those patients graded 4/4 six out of 16 patients did not show ischemic depression in the postexercise ECG He concluded that ST segment change was present only when severe and diffuse coronary artery disease was present

Table II Groups 2 and 3*

				Treadmill exercise stress test													
				Heart rate/min		ST segment changes											
Group	Patient	Age (yr)	Sex	Produced	Achieved	I	II	III	AVR	AVL	AVF	V	V1	V	V	V	V
2	T A S	58	M	169	90		\				\				\		\
	A A M	52	M	173	160		\	\			\					\	\
	R G	51	M	171	149		\	\			\			\	X	\	X
3	D W	47	M	177	150		\	\			\						
	J R	32	M	175	189		\	\			\						

*Group 2, major stenoses of left and right coronary arteries Group 3 primarily right coronary artery disease Abbreviations as in Table I

Table III Groups 4A and 4B*

				Treadmill exercise stress test													
				Heart rate/min		ST segment changes											
Group	Patient	Age (yr)	Sex	90% max predicted	Achieved	I	II	III	AVR	AVL	AVF	V	V	V	V	V	V
4A	E A I	61	M	167	125		\	\			\						
	G N	45	F	179	120		\	\			X						
	J A H	43	M	180	113		\	\			\			\	\	\	\
	D F	49	M	176	145	\	\	\			\		\	\	\	\	\
4B	V D	62	F	167	120									\	\	\	
	J T P	40	M	182	150									\	\	\	\
	H W R	44	M	180	149								\	\	\	\	
	R M	54	M	171	175		X	\								\	\
	G R L	35	M	186	110		\							\	\		
	M C	66	M	163	92		X								\	\	\
	P J	45	M	179	103	\	\	\					X	\	\	\	\

*Group 4A primarily single coronary artery disease with insignificant (< 50% stenosis) in vessel supplying collateral channel
Group 4B severe stenosis (> 90%) in one vessel moderate stenosis (< 90%) in vessel supplying collateral channel (patients G R L and R M included in 4B group because of possibility that the left circumflex was supplying the inferior wall) Abbreviations as in Table I

was 73 per cent of predicted maximal (mean achieved 127 mean predicted 175)

Group 5 (Table IV) is a miscellaneous group in which the ECG changes and coronary arteriographic findings were nonconcordant In patients E H K W K, and H C R coronary artery stenoses were either less than 50 per cent or between 50 and 90 per cent—mild or moderate obstruction and not expected to produce ST segment change In all three cases there was ventriculographic evidence of mitral valve prolapse In patients E W C and J A K the localization of ST segment change could not be clearly related to the coronary artery stenoses and no collateral vessels were demonstrated radiographically to account for nonconcordant ischemic changes Patient A V showed ischemic changes in the inferior leads and in the lateral chest leads with only moderate disease of the right coronary artery and mild disease of left anterior descending and left circumflex Patient E F had significant lesions in both right and left

Prev. infarct	Coronary arteriogram R	LM	LAD	CX	Collaterals	Ventriculogram
	2	0	1	1		0
	1	0	0	1		0 Pr
	1	0	1	2		0 Pr
	0	0	2	0		0 Pr
	3	0	2	1		0
	3	1	2	2		0
	3	1	3	3	RT→CX	1

includes two patients with occlusions of the right coronary artery without ECG or historical evidence of inferior wall myocardial infarction or dyskinesis on ventriculography In both these patients ischemic ST changes were observed only in Leads II III and aV_F

From the data presented in Groups 1 2 and 3 it is apparent that patients with hemodynamically significant stenoses of the left coronary artery the left anterior descending artery or the left circumflex coronary artery show ischemic ST changes primarily in the chest Leads V_2 to V Only four of 16 patients showed changes in the limb leads Patients with exclusive or predominant right coronary artery disease show ischemic ST changes in Leads II III and aV_F and patients with hemodynamically significant stenoses of both right and left coronary artery systems show changes in both the inferior limb leads (II III and aV_F) and in the anterior chest leads

Levin and associates found that in radiographic assessment of coronary arteriograms hemodynamically moderate stenoses (75 to 89 per cent) were virtually never accompanied by collateral vessels In the severe coronary artery stenoses (90 to 99 per cent) collateral vessels were frequently visualized The presence of communicating vessels between the right and left coronary systems is known in neonatal hearts[12] and progressive controlled occlusion of the coronary arteries has led to the development of collateral vessels in the dog heart [1] Baltaxe and Levin and associates[13] have described the anatomy of the collateral circulation as visualized by coronary arteriography In a coronary artery tree with multiple stenoses and occlusions the dynamics of flow will be complex at rest and even more so during exercise when ischemia occurs Local hypoxia is a potent coronary vasodilator and the pressure in the arterial bed distal to a significant stenosis will be further reduced If the distal part of a diseased coronary artery is supplied with a large collateral flow from the other major coronary artery and as blood will flow to the area of lowest resistance it is conceivable that ischemia may result in the territory of the donor vessels supplying the collateral channels This possibility was suggested by Rowe [4] and the term coronary steal applied Groups 4A and 4B represent 11 patients in whom unequivocal ischemic ST segment depression occurs in leads which are nonconcordant with the degree and site of coronary artery stenosis In each of these patients one or more large collateral vessel was demonstrated on coronary arteriography to communicate between the severely diseased vessel and the less severely diseased donor coronary artery In each instance the degree of stenosis of the donor vessel was not sufficiently great to be expected to give ischemic changes Group 5 contains seven patients of whom E F has already been discussed In these patients the ischemic changes occurred with lesser degrees of coronary artery disease than would have been anticipated Three of these patients demonstrated prolapse of the mitral valve a condition which is known to be associated with false positive exercise stress tests In the three remaining patients triple vessel coronary artery disease of mild to moderate severity was present Collateral vessels were not demonstrated radiographically in any patient and the location of ECG change was not concordant with the location of stenoses

Excluding those three patients in Group 5 with prolapsing mitral valve syndrome there was lack of concordance between the ECG changes and the severity and location of coronary artery stenoses in four of 36 patients Twenty one patients (Groups 1 2 and 3) showed changes which were predictable with a knowledge of the coronary anatomy Eleven patients in Groups 4A and 4B showed ischemic changes either in the area of the donor vessel supplying the collateral channels

Table IV Group 5*

Patient	Age (yr)	Sex	Treadmill exercise stress test: Heart rate/min: 90% max predicted	Achieved	ST segment changes: I	II	III	AV_R	AV_L	AV_F	V_1	V_2	V_3	V_4	V_5	V_6
A V	56	M	170	132		\	\			\				\	\	\
F H	58	F	169	129									\	\	\	
K W K	54	M	172	145										\	\	
H C R	38	M	184	166											\	\
F W C	53	M	172	150		X							\	\	\	
J A K	56	M	170	138										\	\	
F F	68	M	161	120								\	\	\	\	\

*Group 5 miscellaneous group where ECG and coronary arteriographic findings were nonconcordant (involving three patients with prolapsing mitral valve syndrome) Abbreviations as in Table I

We have attempted to show that with the use of a 12 lead ECG system and with five separate ECG recordings taken after exercise the ischemic ST changes in many cases are concordant with the location and severity of the coronary artery stenoses

In Groups 1A and 1B (Table I) are patients in whom there is more than 90 per cent stenosis of the left anterior descending coronary artery or patients with between 50 and 90 per cent stenosis of the left main coronary artery In this group three patients had more than 50 per cent stenosis of the right coronary artery In each case this was associated with ECG evidence of an old inferior wall myocardial infarction and a diaphragmatic akinetic or dyskinetic segment on the left ventriculogram If it can be assumed that such dyskinetic areas represent fibrotic scar tissue which would not be expected to show ischemic change then the concordance of left anterior descending or left main coronary artery disease with changes in the anterior chest leads is demonstrated ST segment changes were equally frequent in Leads V_4, V_5 and V_6 (seven out of 10 patients in each case)

In Group 1C, severe stenoses (greater than 90 per cent) were present in the circumflex coronary artery and three of the four patients had total occlusion of the right coronary artery with associated ECG change of old inferior wall myocardial infarction and ventriculographic evidence of diaphragmatic akinesis or dyskinesis If it is again assumed that such fibrotic scar tissue is incapable of showing ischemic change then isolated hemodynamically significant disease of the left circumflex coronary artery produces ischemic ST changes indistinguishable from those of left anterior descending coronary artery disease Changes were equally frequent in Leads V_5 V_4 and V_6 (four of four patients in each case)

A total of four patients showed major stenoses of both the right and left coronary arteries Three of the patients are included in Group 2 and predictably show changes in Leads II III and aV_F and in the anterior chest Leads V_3 through V_6 The one patient in this group who had suffered an old inferior wall myocardial infarction showed only hypokinesis on the left ventriculogram with no evidence of paradoxical movement The right coronary artery was not totally occluded thus patient R G likely represented recanalization of a vessel with a hemodynamically significant stenosis causing inferior wall ischemia Patient E F in Group 5 also had severe disease affecting both right and left coronary arteries, without old infarction or aneurysm This patient showed changes only in the anterior chest leads The graded exercise stress test of this patient was terminated at the end of Stage I (3 minutes) because of chest pain 74 per cent of the predicted heart rate having been achieved It is possible that more severe exercise stress would have revealed ischemic ST segment changes in Leads II III and aV_F in this individual Group 3

Prev infarct	*Coronary arteriogram* R	LM	LAD	CX	Collaterals	Ventriculogram
	2	0	1	1		0
	1	0	0	1		0 Pr
	1	0	1	2		0 Pr
	0	0	2	0		0 Pr
	3	0	2	1		0
	3	1	2	2		0
	3	1	3	3	RT→CX	1

includes two patients with occlusions of the right coronary artery without ECG or historical evidence of inferior wall myocardial infarction or dyskinesis on ventriculography In both these patients ischemic ST changes were observed only in Leads II III and aV_F

From the data presented in Groups 1 2 and 3 it is apparent that patients with hemodynamically significant stenoses of the left coronary artery the left anterior descending artery or the left circumflex coronary artery show ischemic ST changes primarily in the chest Leads V_4 to V Only four of 16 patients showed changes in the limb leads. Patients with exclusive or predominant right coronary artery disease show ischemic ST changes in Leads II III and aV_F and patients with hemodynamically significant stenoses of both right and left coronary artery systems show changes in both the inferior limb leads (II III and aV_F) and in the anterior chest leads

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alone or in both the area of the hemodynamically significant stenosis and the territory of the donor vessels

Summary

In 39 consecutive patients with unequivocally positive postexercise ECG we have correlated the location and severity of the coronary artery stenoses with the ECG leads in which ischemic ST changes occurred

Patients with major stenoses of the right coronary artery with or without disease of the left coronary system showed ischemic ST changes in Leads II, III and aV_F Patients with major stenoses of the left coronary system many of whom had suffered *old inferior wall infarction*, showed ST changes in Leads I, aV_L and the chest leads

A group of 11 patients showed ischemic ST change in leads other than those expected on the basis of the location and severity of coronary artery stenoses In each of these 11 patients large collateral channels were donated by the vessel in whose territory the ischemic changes occurred This finding lends support to the concept of *intercoronary steal during exercise in coronary* artery disease at the same time reducing the value of the postexercise 12 lead ECG in predicting the location and severity of coronary artery stenoses

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Long term survival of elderly patients after pacemaker implantation

Shlomo Amikam, M D
Joseph Lerner, F R C S
Nathan Poguin, M D
Haran Peleg, M D
Egon Riss, M D, M Sc, F A C C
Haifa, Israel

Permanent cardiac pacing has become the accepted therapy for symptomatic atrioventricular block. In recent years the indications have been extended to include other conditions such as sick sinus syndrome, carotid sinus syndrome[3] and certain forms of brady- and tachyarrythmias. The majority of patients requiring pacemaker implantation are in the sixth, seventh, and eighth decades of life, but a significant number of patients are in the younger age groups. So far little attention has been given to the particular problems and outcome of pacemaker implantations in the most advanced age groups.

We have reported previously on the long term survival of 150 consecutive patients with implanted pacemakers. Our results were closely comparable with those of previous similar studies indicating a markedly improved prognosis in these patients.

The purpose of the present report is to focus attention on patients most advanced in age with particular regard to the long term prognosis in this selected group. This series consists of 80 patients who were in the eighth and ninth decades of life at the time of the implantation and who were followed for a period of 1 to 8 years.

Subjects and methods

Patients. Between April 1965 and November 1974, 170 patients underwent pacemaker implantations at the Rambam Government Hospital, Haifa. These patients were followed regularly at the hospital pacemaker clinic at intervals of 3 to 6 months. Of these patients we selected 80 who had been over the age of 70 years at the time of implantation and had been followed for at least 1 year. The average age of this group of patients was 75.4 years, the oldest being 87 years. Table I shows the age distribution of these 80 patients, of whom 50 were male and 30 were female. Twenty-one patients (26.3 per cent) had clinical evidence of coronary heart disease (previous myocardial infarction or angina pectoris), 17 (21.3 per cent) had diabetes mellitus, 67 had atrioventricular block which was considered to be idiopathic, four had sick sinus syndrome. None of the patients in the study had had heart block which developed directly after acute myocardial infarction or cardiac surgery. The electrocardiographic (ECG) findings at the time of implantation were as follows: (1) complete atrioventricular block (permanent or transient) in 59 patients (73.9 per cent); (2) second degree atrioventricular block in 11 patients (13.5 per cent); (3) trifascicular block without evidence of more advanced heart block in six patients (7.6 per cent); (4) ECG findings characteristic of sick sinus syndrome in four (5 per cent).

The indications for pacemaker implantation were based on clinical grounds and were of two kinds: (1) Stokes-Adams attacks which were present in 52 of the cases (65 per cent); (2) symptoms or signs of chronic low cardiac output causing dizziness, fatigue, dyspnea on effort, angina, or overt signs of heart failure which occurred in 28 patients (35 per cent). In no case

From the Department of Cardiology and Cardiac Surgery, Rambam University Hospital, Aba Khoushy School of Medicine, Haifa, Israel.
Received for publication March 11, 1975.
Reprint requests: Dr S Amikam, Department of Cardiology, Rambam Government Hospital, Haifa, Israel.

Table I Age distribution

Age group	*No of patients*
70–74	40
75–79	27
80–84	8
85–87	[illegible]

Table II Causes of death

Cause of death	*No of patients*
I Postoperative death	
Ventricular fibrillation (seventh day)	1
Septicaemia (fifth day)	1
II Late death	
Heart failure	7
Malignancy	3
Complications following fracture of femur	2
Sub arachnoid hemorrhage	1
Cause unknown (death outside hospital)	6
Total	21

Table III Survival rate

Follow up period (yr)	*No of patients*	*No of survivors*	*(%)*
1	80	72	90.0
2	67	55	82.1
3	54	40	74.1
4	37	25	67.2
5	24	14	58.3

was a pacemaker implanted in an asymptomatic patient whatever the ECG findings

Methods During the initial period (1965 to 1967) only epicardial electrodes were used for pacemaker implantation This procedure requires general anesthesia and thoracotomy Since 1968 the transvenous endocardial method of electrode implantation has been employed almost exclusively This procedure requires local anesthesia only and permits an earlier return to activity In this method the endocardial electrode is introduced through the left cephalic vein in the deltopectoral triangle, or by way of another nearby pectoral tributary of the left subclavian vein The pacemaker unit is implanted in a subcutaneous pocket in the left anterior chest wall The unit was implanted in a subpectoral muscle pocket in particularly thin patients (of more frequent occurrence in the elderly) In 67 patients a transvenous endocardial electrode was used, and in 13 patients an epicardial electrode

The pulse generators used were of two* types (1) "fixed rate," implanted in 30 patients, and (2) "demand" (ventricular inhibited) implanted in 50 patients In the initial period only fixed rate pulse generators were used Since 1968 we have used almost exclusively the demand type Presently, whenever a battery replacement is required we usually replace the fixed rate unit with a demand unit, providing that the ventricular excitation threshold is satisfactory

Results

Deaths There were 21 deaths in this group of 80 patients two patients (2.5 per cent) died during the immediate postoperative period and 19 patients during a period of 3 months to 6 years after the implantation The causes of death are listed in Table II

Of the two patients who died in the immediate postoperative period one developed ventricular fibrillation on the seventh postoperative day following demand endocardial pacemaker implantation, which was resistant to repeated attempts of DC defibrillations The second patient was a 70 year old diabetic woman who developed local infection at the site of the implanted epicardial pacemaker unit with subsequent purulent pericarditis and septicaemia

Of the 19 patients who died in the follow up period causes of death are known to us in 13 In six patients who died outside the hospital the cause of death is uncertain In these patients the possibility that death was due to failure of one of the pacemaker components cannot be ruled out, however it was not the cause in any of the 13 known cases

Survival All patients were followed for at least 1 year after the pacemaker implantation, 67 of these could be followed up for 2 years, 54 for 3 years 37 for 4 years, and 24 for 5 years after implantation Table III shows the survival rates in these groups of patients At present we have in our follow up two patients who are alive 6 years after implantation, three patients, 7 years after implantation three patients 8 years after implan

*Medtronic models nos 5860 5860 C 58?? C 5841 5842 594?

tation all were at least 70 years old at the time of the implantation

Complications Twelve of the 13 patients with epicardial pacemakers survived the operation Of the survivors nine patients required readmission during the follow up period because of recurrence of symptoms due to cessation of pacing The causes were fracture of epicardial electrode (three patients—in one patient two episodes) elevated stimulation threshold (two patients) and early failure of battery (four patients) It should be noted that early battery failure occurred only in the initial years (1966 to 1969)

Sixty six of the 67 patients with endocardial pacemakers survived the operation Of the survivors cessation of pacing occured in 18 patients The causes were displacement of endocardial electrode tip (14 patients—in three of them it caused in addition perforation of the myocardium) exit block (three patients) and faulty connection between pacemaker unit and electrode (one patient) Other complications which appeared during the follow up period in the endocardial group but did not interfere with pacing were local hematoma at implant site (six patients) skin erosion due to pressure of the implanted unit (three patients) and local infection at implant site (three patients) In three patients satisfactory long term pacing was obtained with an endocardial electrode placed in the coronary sinus Only in one case of the endocardial group early battery failure appeared (year 1971) None of the complications listed above caused death The postoperative and late complications are summarized in Table IV

The most common complication was displacement of the endocardial electrode It occurred most frequently in the early years of our endocardial pacemaker experience but became rare in recent years

Morbidity Of the 61 surviving patients being followed by us, 42 are enjoying good health and are normally active for their age Some of them still do a full day s work Nineteen patients are limited in their activity but still are able to live independently none of them being bedridden or requiring nursing assistance Thirty patients of the 61 are receiving therapy for congestive heart failure which is mild in half of them and of moderate to severe in the rest

Five of our patients underwent successful surgery since the pacemaker implantation one patient had laparotomy for polyposis of the colon one patient had cystostomy with resection of carcinoma of the bladder one patient had a cataract extraction and two patients underwent prostatectomy Two patients are psychotic and have frequent admissions to mental institutes It is of interest that none of 61 survivors and the 13 patients who died in whom the cause of death is known suffered an acute myocardial infarction or cerebrovascular event since the pacemaker implantation

Table IV Complications

Complications	*No of episodes*
Epicardial electrode (total 13 patients)	
Fracture of electrode	4
Threshold elevation	2
Early battery failure	4
Total	10
Endocardial electrode (total 67 patients)	
Displacement of electrode	11
Perforation	3
Exit block	3
Faulty connection between battery and electrode	1
Early failure of battery	1
Hematoma at implantation site	6
Skin erosion over implantation site	3
Local infection at implantation site	3
Total	31

Discussion

The mortality rate in patients who suffered Stokes Adams attacks due to complete A V block, treated medically was reported to be 50 per cent within the first year since the onset of clinical manifestations and 75 per cent within 5 years [12] The introduction of pacemakers changed dramatically the course of this disease Presently 80 to 90 per cent of these patients can expect to survive 1 year following pace maker implantation and 50 to 60 per cent can expect to remain alive 5 years thereafter In a previous study[4] we reported on the survival rate of 150 patients who had been followed for a period of 1 to 5 years after pacemaker implantation 90 1 per cent survived 1 year after implantation 82 4 per cent 2 years 75 4 per cent 3 years 70.5 per cent 4 years 66 7 per cent were alive out of the group which had been followed for 5 years We assumed

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85 87	5

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Of the two patients who died in the immediate postoperative period one developed ventricular fibrillation on the seventh postoperative day, following demand endocardial pacemaker implantation, which was resistant to repeated attempts of DC defibrillations The second patient was a 70 year old diabetic woman who developed local infection at the site of the implanted epicardial pacemaker unit, with subsequent purulent pericarditis and septicaemia

Of the 19 patients who died in the follow up period causes of death are known to us in 13 In six patients who died outside the hospital the cause of death is uncertain In these patients the possibility that death was due to failure of one of the pacemaker components cannot be ruled out, however it was not the cause in any of the 13 known cases

Survival All patients were followed for at least 1 year after the pacemaker implantation 67 of these could be followed up for 2 years 54 for 3 years 37 for 4 years and 24 for 5 years after implantation Table III shows the survival rates in these groups of patients At present we have in our follow up two patients who are alive 6 years after implantation three patients 7 years after implantation three patients 8 years after implan

*Medtronic models no 5860 5860-C 5812 C 5941 5842 5942

Summary

The follow up of 80 patients above the age of 70 years with implanted pacemakers is described These patients were the most advanced in age from a total group of 150 with implanted pace makers Their ages ranged from 70 to 87 years with an average of 75 4 years 50 were male and 30 were female An epicardial electrode was implanted in 13 patients and an endocardial electrode in 67 The pacemaker was implanted in 76 patients for symptomatic atrioventricular block and in four patients for sick sinus syndrome Two patients (2 [illegible] per cent) died during the postoperative period and 19 patients within a period of 3 months to 6 years after the implanta tion The survival rates were 1 year 90 0 per cent 2 years 82 1 per cent 3 years 74 1 per cent 4 years 67 2 per cent 5 years 58 3 per cent These survival rates were surprisingly similar for the first 3 years of follow up, to those of our and others previous studies which included all age groups The survival rates in the most advanced age groups decreased in comparison only in the fourth and fifth years after the implantation There was no evidence of new episodes of myocar dial infarction among this group of patients during the follow up period

We conclude that even in patients of the most advanced age groups the implantation of an endocardial pacemaker significantly prolongs life improves its quality and this at a low operative risk

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that the higher survival rate in our series as compared with other similar studies was due to the fact that our series included a relatively high proportion of young patients with congenital heart block In the present study we selected the patients of the most advanced age group The long term follow up survival rates were surprisingly similar to those of our study which included all age groups for the first 3 years of follow up (90 0 82 1, and 74 1 per cent respectively) Only in the fourth and fifth years after implantation did the survival rates in the most advanced age groups decrease compared to the rates in all age groups (67 2 and 58 2 per cent respectively) as could be anticipated from the natural life expectancy in this age group These results indicate that permanent pacing in the elderly patient is justified not only for the immediate need to manage an acute situation (Stokes Adams syndrome) but also because it significantly prolongs life Little attention has been paid to this aspect of pacemaker implantation, and we could find only one comment on this subject in the current literature Obel Marchand and Scott Millar[13] pointed out that in their series of 120 patients Pacing the elderly was at least as rewarding as the younger group

We believe that the main reason for these encouraging results has been the introduction of the transvenous endocardial electrode in pacemaker implantation This method does not require general anesthesia and thoracotomy and has therefore greatly reduced the operative risk This method also allows early mobilization which has a special significance in this group of patients Regular supervision in a special pacemaker clinic is mandatory and provides early detection of battery depletion or other pacemaker malfunctions, e g failure to pace failure to sense fracture or displacement of electrode skin erosion, etc treatment can thus begin at an early stage

The complications associated with the endocardial electrode were displacement perforation exit block, skin erosion, and local infection The complications of the epicardial group were fracture of the electrode and elevation of stimulation threshold These complications were frequent but they were easily corrected and proved fatal in only one case of generalized sepsis in a diabetic patient of the epicardial group The two groups are not comparable with regard to the postoperative mortality rate and the long term complication incidence This is because most of our epicardial implantations were done in the early years of our experience whereas the endocardial implantation were performed mostly in recent years Furthermore, presently the endocardial method enables pacemaker implantation in patients who probably would have been rejected if the epicardial method had been the only one available The incidence of postoperative complications decreased steadily over the years, presumably as a result of increased experience and improved technical reliability of the pacemakers An innovation which reduced markedly electrode tip displacement was the use of a butterfly anchor thus ensuring good fixation of the endocardial electrode to the vein of introduction

Davidson and associates[11] investigated the incidence of myocardial infarction and cerebrovascular accidents over a prolonged period following pacemaker implantation They showed that there was no increase in the incidence of these episodes as compared to the expected incidence for this age group We can support these findings as we have not seen a case of myocardial infarction or cerebrovascular accident among our 80 patients (except for one death from subarachnoid hemorrhage) In a significant number of patients in whom the pacemaker was implanted because of Stokes Adams attacks congestive heart failure appeared during the follow up period In patients in whom refractory congestive heart failure with complete heart block was the indication for pacing improvement of the heart failure was usually achieved

We became convinced that the quality of life in the elderly patient suffering from atrioventricular block is much improved following implantation These patients become again independent for their daily needs their mental processes are preserved, and some of them are even able to continue working far beyond the age of retirement All these benefits are in addition to the relief from a constant fear of a recurrence of a Stokes Adams attack

We conclude that pacemaker implantation in the most elderly patients with complete heart block is beneficial not only for the treatment of the acute problem but also because it prolongs life and greatly enhances its quality The dependence of these previously gravely disabled patients on their families and society is thus reduced

Table I Aneurysms of membraneous septum

Cases	Age (yr)	Volume	Smooth borders	Large pedicle	Image of contrast jet in systole	Associated lesions	Surgery	Miscellaneous
1	7	Small	+	+	+		–	
2	6	Fairly large	+	+	– right ventricle opacified		–	
3	5	Large	+	+	+		–	
4	5½	Fairly large	+	+	+		–	
5	8	Large	Irregular polylobulated	+	+	ASD	–	
6	13	Large	+	+	+	Small aortic dextroposition	–	
7	[illegible]	Fairly large	+	+	+	Muscular VSD aortic insufficiency aortic dextroposition	–	
8	3	Large	+	+	– right ventricle opacified	Muscular VSD	+	Hemiplegia
9	7	Middle size	+ or –	+	+		–	
10	8	Large	+ but polylobulated	+	+ double	Pulmonary infundibular stenosis	–	
11	11	Small	±	+	+	Aortic dysplasia kinking and dilated sinuses of Valsalva	–	Dilated sinus hides M.S.A
[illegible]	13	Large	±	+	+	ASD aortic dextroposition	–	
13	8 m	Small	+ nipple aspect	+	–	Trisomy 21 ASD	–	
14	[illegible]	Large	+	Narrow	–	Polymalformative syndrome	–	Defect of pulmonary infundibulum MSA fistulated in right atrium
15	7	Large	Irregular polylobulated	+	–	ASD	+	Postoperative aortic insufficiency
16	23	Fairly large	+	+	–	Infundibular and midventricular severe stenosis	+	
17	7 mos	Fairly large	Irregular	+	–	ASD membraneous VSD below the MSA	–	
18	28	Very large	+	+	–	Aortic insufficiency direct communication left ventricle–right atrium	+	Difficult diagnosis MSA communication left ventricle right atrium

very sharp but it is sometimes difficult to define the superior border which can form a blur with the anterior coronary sinus Generally the aneurysmal pouch has a large pedicle (17 out of 18 cases) and smooth borders (12 out of 18 cases) In some cases however the borders are not sufficiently sharp and cannot be seen well Twice we have seen a small nipple shaped outgrowth at the tip of the aneurysmal pouch (Fig 3) The size of the aneurysm is variable It is much larger in systole than in diastole where it can even disappear The aneurysm was small (Fig 4) in three cases and large (Figs 5 to 7) in the remaining cases The image of the contrast jet in systole has

Radiologic patterns of aneurysms of the membraneous septum

J C Hoeffel
M Henry
M Flizot
R Lucen
C Pernot
Nancy France

Aneurysms of the membraneous septum occur mainly in spontaneous closure or reduction of ventricular septal defect (VSD) The systolic pressure gradient between both ventricles causes bulging into the right ventricle which in turn favors proliferation of a fibrous collar

This type of aneurysm can be seen in congenital deficiency of the membraneous septum without VSD The membrane can be distended and can even perforate thus creating the VSD frequently seen in this case In reality the aneurysm of the membraneous septum is usually associated with a small VSD In this type of defect however the process is different the aneurysm is associated with a formerly large VSD which has been reduced

Many authors support this theory—Freedom and associates[11] in their large series and ourselves

Aneurysm of the membraneous septum is usually visible in systole It is essentially a radiologic entity much more than an anatomic one to the extent that some cases have not even been discovered during open heart surgery Sometimes the lesion is not really a septal aneurysm but a pouch which develops from the septal leaflet of the tricuspid valve which adheres to the VSD however the angiocardiographic features are similar We report eighteen cases of MSA 15 children between 2 and 13 years of age an infant of 7 months and two adults aged 23 and 28 (Table I)

The natural history is uniform In infants we usually encountered large and severe VSDs which later regressed with decreasing cardiomegaly on the plain chest film The clinical features are very similar to those of VSD Among the usual diagnostic tools only the phonocardiogram is evocative The recording of a two component systolic murmur (7 out of 18 of our cases) is very typical one is protosystolic of low amplitude followed by a more ample mesosystolic component In four cases out of seven a click was associated with the murmur This pattern can be explained by the tension of the aneurysm during ventricular systole The first part of the murmur reflects blood flow from left ventricle to aneurysm the second reflects blood flow through the perforated aneurysm maximally dilated in mid and telesystole The discovery of this murmur is of great value especially if a holosystolic regurgitation murmur has been recorded some years earlier in the same child

Left ventriculography

Left ventricular cineangiography in the lateral view is the principal method which permits firm diagnosis of aneurysm

The aneurysm appears as a round bulge (Fig 1) sometimes lobulated (Fig 2) (3 out of 18 cases) at the level of the membraneous septum just beneath the right anterior coronary sinus The aneurysm is maximally dilated during ventricular protosystole and it disappears more or less during diastole The inferior border is always

From the Departments of Cardiology and of Radiology Hôpital Jeanne d Arc Dommartin les Toul Paris France

Received for publication March 13 19

Reprint requests J C Hoeffel M D Department of Radiology Hôpital Jeanne d Arc 54 Dommartin les Toul France

Fig 5 [redacted] year-old patient Case 18 Lateral view of left ventriculography Large aneurysm with smooth borders Associated aortic insufficiency

Fig 6 5-year old patient Case 3 Lateral view of left ventriculography Large aneurysm with jet of contrast medium on systole

been noted in 10 cases and in one case there were two jets (Fig 8) At times the jet [redacted] not visible but the right ventricle is opacified confirming its presence (two cases)

We have not noted the so called wind sock pattern type D of Varghese and associates In one case the aneurysm bulged into the right cavities (case 14) and an infundibular defect was seen on the lateral view in right ventriculography

Angiography is also helpful to diagnose frequently associated lesions

Dextroposition of the aorta (Fig 1) was seen in three cases and generally is fairly frequent [redacted] [3] It is visible in lateral left ventriculography in systole The pathogenic importance of dextroposition has been explained by Lev and Saphir [8] They felt that horizontalization of the pars membranacea causes aneurysmal distension under high ventricular pressure

Other associated lesions are secondary to long evolving VSD s This is true for pulmonary infundibular stenosis right midventricular stenosis (1 out of 18) aortic insufficiency (2 out of 18) and tricuspid insufficiency

We have also noted dilatation of the right anterior sinus of Valsalva with kinking (or aortic pseudocoarctation) five atrial septal defects (ASD) one muscular VSD one membraneous septal defect beneath the MSA and a polymalformative syndrome

Complications and course of aneurysms of the membraneous septum

Some complications are possible and have no radiologic feature. These include infectious endocarditis and conduction arrhythmias due to close proximity of His bundle and its branches We also had one case of intrasaccular thrombosis with rapidly appearing hemiplegia secondary to embolism in a 3 year old child In our opinion angiography should be performed each time hemiplegia appears without any evident causes The finding may well be an aneurysm of the intracardiac septa

Other complications usually have radiologic features

Obstruction of the right ventricular outflow tract is frequent [7, 8] In one case we found right midventricular stenosis (Fig 9) with a pressure

Fig 1 13 year old patient Case 12 Left ventriculography lateral view Aneurysm of large size with a large pedicle aortic dextroposition

Fig 3 8½ year old patient Case 13 Lateral view of left ventriculography Small aneurysm with nipple image

Fig 2 8 year old patient Case 5 Lateral view of left ventriculography Large polylobulated aneurysm with large pedicle

Fig 4 7 year old patient Case 1 Lateral view of left ventriculography Small aneurysm with smooth border and a large pedicle The jet of contrast material is well seen

Fig 9 23-year-old patient Case 16 Lateral view of right ventriculography Infundibular and tight mid ventricular right stenosis with an aneurysm of membraneous septum

that confusion between a sinus of Valsalva aneurysm and MSA is possible even at surgery

Partial or total adhesion of the septal leaflet of the tricuspid valve to the edge of the VSD presents as an aneurysmal pouch which is impossible to differentiate from MSA

A VSD closed surgically may sometimes appear as a semicircular pouch and the pattern is fairly similar to MSA but the clinical history is different

Diagnosis is also very difficult when an aneurysm of the sinus of Valsalva ruptures into the right cavities Selective aortic opacification is necessary to differentiate the jet image from that of a VSD Radiologic criteria are as follows the sinuses are deformed especially the anterior right sinus which is dilated and prolapsed The jet of contrast medium has a direction slightly oblique anteriorly and downward and is localized at a higher level than that of VSD with aortic insufficiency The right cavities may be opacified abnormally the rupture taking place in the right ventricle or in the right atrium

Other differential diagnoses include aortic insufficiency with prolapse of the tricuspid septal leaflet through a VSD aneurysm of a coronary artery, mainly the right which may rupture into the left ventricle rendering the diagnosis difficult and the aortic–left ventricular tunnel which arises above the right coronary artery

Treatment

It is important to emphasize that MSA often reflects an initially large VSD which gradually closes Prognosis is good but there are some particular hazards In uncomplicated and well tolerated cases regular medical checkups usually suffice Treatment of the rare complications depends on the type Systematic surgical excision is unnecessary Indeed, if the aneurysm is small even in systole the surgeon may not even see it Though surgical indications are not uniform the techniques are the same resection of the pouch direct suture or Teflon patch

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Fig 7 13 year old patient Case 6 Oblique left anterior view of left ventriculography Large aneurysm of membraneous septum

Fig 8 8 year old patient Case 10 Lateral view of left ventriculography Polylobulated huge aneurysm with double jet of contrast medium on systole

gradient in a 23 year old patient though in six other cases we recorded an infundibular gradient without radiologic signs of stenosis

Aortic insufficiency is well known in the course of VSD and can develop more easily if there is an aneurysm of the membraneous septum Valvular eversion causes severe aortic insufficiency often ending in severe failure and death We have noted two cases of mild aortic insufficiency

Although no cases were observed in our series tricuspid insufficiency is not a rare complication It can be explained by adhesion between the aneurysmal pouch and the septal tricuspid leaflet or by protrusion of the aneurysm through the tricuspid annulas

In general however despite the numerous possibilities complications occur infrequently during the course of aneurysms of membraneous septum

Uncomplicated cases are well tolerated and aneurysms of membraneous septum have been discovered at autopsy in patients of 70 years or more

Differential diagnosis

In cases of aortic insufficiency, the diagnosis may be very difficult

When there is no aortic insufficiency, the primary differential diagnosis is dilatation of the sinus of Valsalva In such cases aortography is very useful in delineating the inferior border of the sinus On left ventriculography the dilated sinus is opacified at the same time as the ascending aorta and not before the aorta The diagnostic difficulty increases if both defects are associated as in one of our cases where dilatation of the anterior intracoronary sinus hid the MSA (case 11) In other cases as Soulie and associates[13] pointed out, the aneurysm of the sinus of Valsalva may dissect the membraneous septum and protrude through an associated VSD The angiographic pattern may be so similar to MSA

Experimental and laboratory reports

Initial adjustment of cardiac output in response to onset of exercise in patients with chronic pacemaking as studied by the measurement of pulmonary blood flow

Tomiyasu Koyama
Susumu Nakajima
Masashi Horimoto
Sapporo, Japan

The increase in cardiac output of normal human subjects during exercise is mainly supported by an increment in heart rate. It was observed in dogs with denervated cardiac nerves, however, that the cardiac output was quickly augmented despite the slow rise in heart rate. It was therefore of great interest to study the rate of increase in cardiac output at the beginning of exercise in human patients whose heart rate could not change quickly because of heart block and an implanted pacemaker.

In previous publications, a technique was introduced to determine changes in pulmonary blood flow during transient states such as the beginning of exercise or elevation of intrathoracic pressure. The technique consisted of the rapid inhalation of a low concentration C_2H_2 gas mixture, the expiration of the mixture at a constant flow rate, and continuous analysis of C_2H_2 fraction in the expired gas by the use of a glow discharge rapid gas analyser. Since the *rate of decrease in the C_2H_2 fraction* depended on pulmonary blood flow and pulmonary gas volume, the pulmonary blood flow for each sequential small time interval could be detected from the continuous recording of the C_2H_2 fraction in the expired gas.

Five patients with a chronically implanted pacemaker, Medtronic 5942 (Table I), inhaled a 4.4 per cent C_2H_2 mixture in an upright position quietly standing on a treadmill and exhaled the pulmonary gas at a rate of 50 to 90 ml. per second for 7 to 10 seconds. Then the treadmill started moving at the rate of 5 km. per hour with 0 per cent grade. The patients exercised lightly on the treadmill while maintaining a constant rate of expiration. The heart rate was monitored with microwave transmitted precordial electrocardiography. The patients received only oral instructions and practically no training *for the start of* the treadmill movement.

An actual recording is shown in Fig. 1, where the curves above and below show the expiration rate and C_2H_2 fraction, respectively, in the expired gas. In Fig. 1, *A*, the patient remained quietly standing throughout the whole process of expiration. The C_2H_2 curve showed a peak because of the washout of the gas mixture filling the dead space and thereafter declined smoothly. In Fig. 1, *B*, the patient exhaled for the first 10 seconds in a quiet state and then started the mild treadmill running. Soon after the onset of exercise the decay rate of the C_2H_2 curve showed a sudden increase, suggesting a rapid augmentation of pulmonary blood flow. The lag time between the start of exercise and the sharp decline of the C_2H_2 curve was mainly explained by the washout time of the dead space gas and, in addition, by a small delay in the increment of cardiac output following the onset of the exercise (1.5 seconds on average). Meanwhile the heart rate showed only a slight increase—from 63 to 65 beats per minute over the time length of the observation. The

From the Division of Physiology, Research Institute of Applied Electricity, Hokkaido University, Sapporo, Japan.

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Reprint requests: Tomiyasu Koyama, Hokkaido University, Research Institute of Applied Electricity, Sapporo, Japan.

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From the Division of Physiology Research Institute of Applied Electricity Hokkaido University Sapporo Japan

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Reprint requests Tomiyasu Koyama Hokkaido University Research Institute of Applied Electricity Sapporo Japan

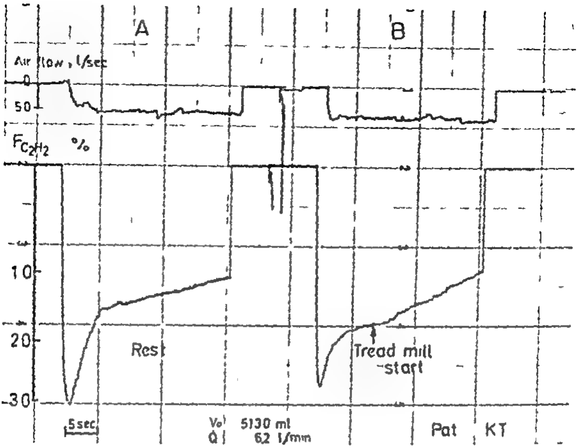

Fig 1 An example of actual recording of C_2H_2 fraction in the expired gas A standing quietly B treadmill running was started in the course of continuous expiration

Table 1 The patients

Pt	Age (yr)	Sex	Diagnosis	Date of pacemaker implant	Date of measurement	Basic heart rate (b.p.m.)	Remarks on ECG
K T	52	M	Complete A V block	April 24 1971	July 3 1973	63	Heart rate increased to 65
K Ku	53	F	2 1 A V block	Aug 25 1971	Sept 6 1973	70	ECG partially replaced by sinus rhythms but heart rate remained almost unchanged
M S	50	M	Complete A V block	Oct [illegible] 1972	Feb 27 1974	70	Ditto
K Ka	53	M	Ditto	Sept 2 1972	Feb 27 1974	70	Ditto
C I	64	F	Sick sinus syndrome	June 7 1973	June 19 1973	70	Ditto

pulmonary blood flow sequentially calculated for each 2.5 seconds interval is summarized in Fig 2 In four patients except C I, who had received the surgical treatment for pacemaker implantation only 12 days previously, pulmonary blood flow showed a rapid increase at the onset of exercise though there was a large scatter between individuals

Our observations in the present study were restricted to the first 10 seconds of transient increase in cardiac output and were not extended beyond this period because of recirculation [2] But in any event although the number of patients studied is still small it is probable that stroke volume could increase rapidly also in human subjects at the start of exercise resulting in a quick increment of cardiac output In connection with this observation on the transient changes it

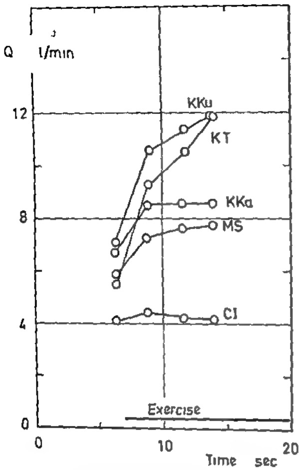

Fig 2 Transient change in pulmonary blood flow after the onset of treadmill running calculated from the C_2H_2 fraction curve

must be mentioned that a significant increase of cardiac output is well known during steady exercise in patients whose heart rate was maintained at a constant rate [8] The most likely explanation for this increment in stroke volume may be the Starling mechanism and nervously triggered quick decrease in peripheral vascular tone [9]

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Facilitation of A-V nodal reciprocation by procainamide

Ramon A. Fabregas, M.D.
Jaok Han, M.D., Ph.D.
Brij G. Goel, M.D.
Myung S. Yoon, M.D.
Albany, N. Y.

Reciprocal or echo beats can be produced in the ventricle by early premature ventricular beats, and the occurrence of these reciprocal beats has been attributed to longitudinal dissociation of the atrioventricular (A-V) node into two pathways.[1-4] These dual pathways having different refractory periods permit an early ventricular beat to propagate from the ventricle to atrium over one pathway and to return to the ventricle over the other to produce an echo or reciprocal beat. Sustained reciprocation of an impulse through the A-V node has long been considered as a likely explanation of paroxysmal supraventricular tachycardia.

Mendez and associates have shown that there is a continuous range of the coupling intervals of ventricular premature beats (or an "echo zone") within which ventricular echoes can be induced in experimental dogs. They also showed that A-V nodal reciprocation is facilitated and the echo zone is widened under the influence of some of the conditions which increase the refractory period and depress conduction in the A-V node. Procainamide is known to increase the A-V nodal refractory period and conduction time. This agent is therefore expected to facilitate the occurrence of A-V nodal reciprocation. The present study was undertaken to demonstrate this potentially deleterious effect of procainamide on A-V nodal reciprocation in dog hearts.

From the Department of Medicine (Cardiology), Albany Medical College of Union University and the Electrocardiography Laboratory, Albany Medical Center Hospital, Albany, N. Y.

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Reprint requests: Jaok Han, M.D., Department of Medicine, Albany Medical College, Albany, N. Y. 12208.

Methods

The experiments were conducted on mongrel dogs weighing 10 to 15 kilograms and anesthetized by intravenous injection of sodium pentobarbital in a dose of 30 to 35 mg. per kilogram. Under artificial respiration the thorax was opened in the midline, and the heart was exposed and suspended in the opened pericardium. The sinoatrial node was crushed and the heart was driven at a constant rate by electrical stimuli applied to the right ventricle. A femoral artery was cannulated to record the arterial pressure and to obtain blood samples for the determination of blood gas and blood levels of procainamide. A femoral vein was also cannulated for the administration of procainamide. Arterial blood gas and pH were frequently checked and were corrected if needed.

The bipolar stimulating and recording electrodes were small steel hooks with an interelectrode distance of 2 to 3 mm. The stimulating electrodes were attached to the anterior septal margin of the right ventricle. The recording electrodes were attached to the anterior surface of both the right atrium and the right ventricle. A Lead II electrocardiogram (ECG), local electrograms from the right atrium and the right ventricle, and the artifact of stimuli delivered to the right ventricular stimulating electrodes were all recorded on an Electronics for Medicine recorder at a paper speed of 100 mm. per second. Pacing and premature stimuli applied through the stimulating electrodes were 2 msec. in duration and twice the diastolic threshold. The patterns of these stimuli were programmed with a variable

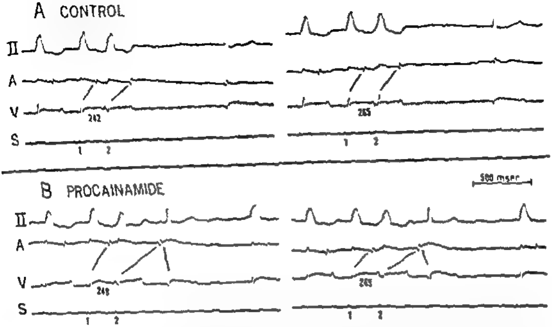

Fig 1 Development of ventricular echoes after the administration of procainamide Panel *A* in the control state and B after procainamide Tracings are Lead II ECG s local electrograms from the right atrium (*A*) and the right ventricle (*V*) and the artefact of stimuli (S) applied to the right ventricle The ventricle was paced by basic stimuli (S) and ventricular premature beats were induced by premature stimuli (S) applied at various coupling intervals See text for detailed description

interval generator and a series of Tektronix pulse generators

The ventricles were paced at a cycle length of 400 msec after the last of a series of 10 paced beats (V) ventricular premature beats (V) were introduced at various coupling intervals (V,V) Ventricular pacing wa interrupted for about 1 5 seconds following each premature V_2 to observe the appearance of ventricular reciprocal beats Retrograde conduction times of these premature V (V A, intervals) and the corresponding A_1A_2 intervals were measured When ventricular reciprocal beats or echoes (V) appeared following premature V conduction times of V from the atrium to ventricle (A V intervals) and the corresponding intervals between premature V_2 and V (V V intervals) were also measured The functional refractory period of the A V node was recorded as the minimal interval between two atrial responses (the shortest A A) both propagated from the ventricle

Results

The effect of procainamide on A V nodal reciprocation was studied in 20 dogs The drug was given intravenously in a bolus injection of 10 mg per kilogram of body weight In these animals blood levels of the drug immediately reached the peak of 20 to 32 µg per milliliter fell to therapeutic levels of 4 to 9 µg per milliliter in about 25 minutes and remained at these levels throughout the period of blood level determination up to 60 minutes after the injection The effect of procainamide was tested about 30 minutes after the injection No ventricular reciprocal beats occurred in a group of eight dogs in the control state and the reciprocal beats appeared in five of the eight dogs after the administration of procainamide The reciprocal beats occurred in another group of 12 dogs in the control state the occurrence of these echo beats became more frequent after the administration of procainamide in 10 of the 12 dogs

Fig 1 illustrates the results of one of those experiments in which ventricular reciprocal beats appeared after the administration of procainamide In the control state in panel *A* early premature beats (V_2) were introduced at the coupling intervals (V_1V_2) between 242 and 265 msec and these premature V_2 were propagated to

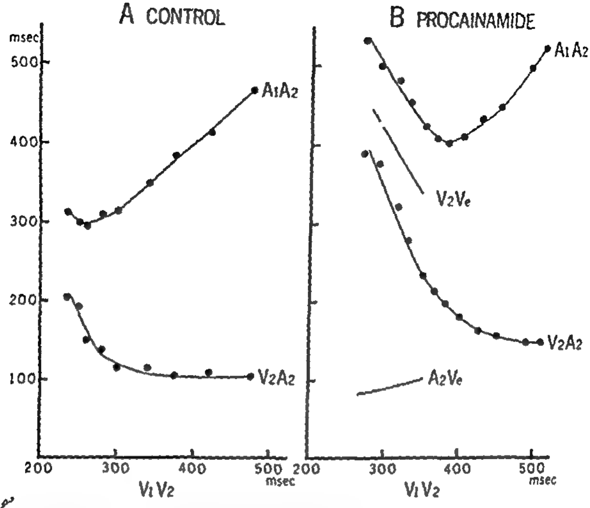

Fig 2 Development of ventricular echoes after the administration of procainamide Graph A in the control state and B after procainamide V V_2 intervals are plotted on the abscissa and the corresponding V A A_1A_2 A V and V V intervals on the ordinate See text for detailed description

the atrium but failed to induce ventricular reciprocal beats The earliest possible retrograde propagation occurred with a V_2A_2 interval of 208 msec at a V_1V_2 interval of 242 msec In panel *B* after the administration of procainamide, early premature V at V_1V_2 intervals of 248 to 265 msec were followed by ventricular reciprocal beats or echoes The echo zone as measured as the range of V_1V_2 intervals at which the reciprocal beats occurred was 17 msec It should be noted that premature V_2 were propagated to the atrium more slowly with longer V_2A_2 intervals in comparison with those in the control state The earliest effective V_2 at a V_1V_2 interval of 248 msec was conducted to the atrium with a much longer V_2A_2 interval of 385 msec The results indicate that slow retrograde conduction through the A V node facilitated the appearance of ventricular reciprocal beats after procainamide was administered to the animal

Fig 3 depicts the appearance of ventricular reciprocal beats after the administration of procainamide in another dog In the control state in Fig 2, *A* the V_1V_2 intervals were plotted on the abscissa, and retrograde conduction times (VA_2 intervals) of premature V_2 and the corresponding A_1A_2 intervals were plotted on the ordinate Late premature V_2 with longer V_1V_2 intervals (> 300 msec) were propagated to the atrium with V_2A_2 conduction intervals equal to that of the basic ventricular response at about 105 to 115 msec This resulted into the equality between V_1V_2 and A_1A intervals and the points for A_1A_2 intervals fell on a 45° line on the graph As the V_1V_2 intervals were gradually reduced below 300 msec, early premature V_2 were propagated to the atrium more slowly resulting into a gradual increase in the V_2A_2 interval and a corresponding increase in the A_1A_2 interval at the left hand of the graph The earliest possible retrograde conduction occurred at a V_1V_2 interval of 240 msec with a V_2A_2 interval of 205 msec The

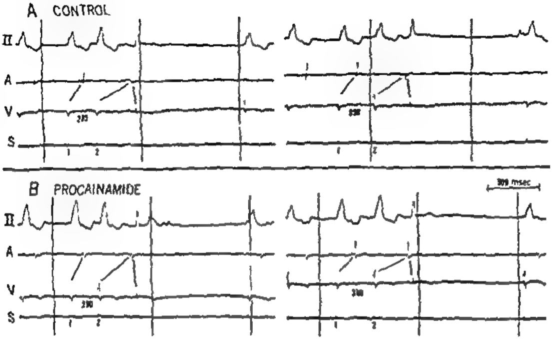

Fig 3 Increase in ventricular echo zone after the administration of procainamide Conventions as in Fig 1 See text for detailed description

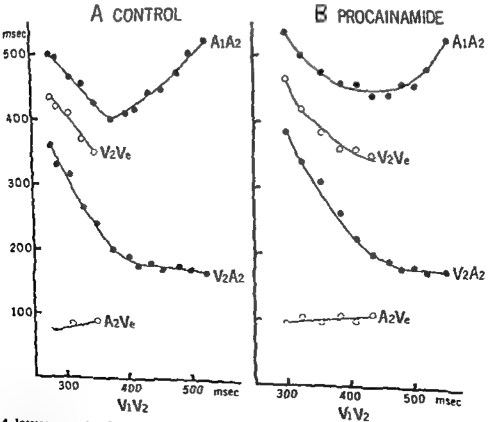

Fig 4 Increase in ventricular echo zone after the administration of procainamide Conventions as in Fig 2 See text for detailed description.

Table I Effect of procainamide on ventricular echo zone

Exp No	Echo zone (msec)	
	Control	Procainamide
Group I		
1	0	17
2	0	38
3	0	0
4	0	0
5	0	90
6	0	33
7	0	0
8	0	56
Mean	0	29 3
Group II		
1	35	90
2	18	43
3	65	90
4	12	40
5	48	70
6	23	62
7	15	42
8	46	46
9	20	38
10	58	58
11	40	95
12	80	140
Mean	38.3	67 8

functional refractory period of the A V node as measured as the shortest possible A_1A_2 interval, was 295 msec In the control state, however, no reciprocal beats could be induced by early premature beats

In the same experiment as in Fig 2 *A* ventricular reciprocal beats (V) appeared after the administration of procainamide Plotted in Fig 2 *B*, are the temporal relationships between V_1V_2 intervals (on the abscissa) and the corresponding V_2A_2, A_1A_2, A_2V_e intervals (on the ordinate) In comparison with the control in Fig 2 *A*, the V_2A_2 and A_1A_2 curves are displaced upward indicating slower conduction of premature V_2 through the A V node to the atrium The functional refractory period of the A V node also increased as indicated by an increase in the shortest A_1A_2 interval to 405 msec Ventricular reciprocal beats (V_e) were regularly induced by early premature V_2 at V_1V_2 intervals of 270 to 360 msec with an echo zone of 90 msec These reciprocal beats occurred when the retrograde conduction of early premature V_2 was markedly delayed resulting into a marked increase in the V_2A_2 and A_1A_2 intervals at the left hand limbs of these two curves Conduction times of returning echo beats (or A_2V_e intervals) were not markedly variable The curve for V_2V intervals was obviously determined by the V_2A_2 intervals and the V_2V_e interval increased with the increase in V_2A_2 interval

Fig 3 illustrates the results of one of those experiments in which returning ventricular echoes became more frequent and the echo zone was widened after the administration of procainamide In the control state in panel *A*, ventricular reciprocal beats could be induced by early premature V_2 introduced at V_1V_2 intervals between 285 and 350 msec (an echo zone of 65 msec) In panel *B*, after procainamide was given to the animal ventricular echoes occurred at V_1V_2 intervals between 290 and 380 msec (an increase in the echo zone to 90 msec) In comparison with the control most of the premature V_2 were conducted more slowly with longer V_2A_2 intervals For example, the V_2A_2 interval of the latest effective premature V_2 was 290 msec in the control and 325 msec after the administration of procainamide

Fig 4 depicts the effect of procainamide in increasing the echo zone in another dog The temporal relationships between the V_1V_2 interval and V_2A_2 A_1A_2, A_2V and V_2V_e intervals were again plotted on the graphs In the control state in part *A* ventricular reciprocal beats occurred at V_1V_2 intervals between 280 and 360 msec (an echo zone of 80 msec) when conduction of early premature V_2 to the atrium were markedly delayed as indicated by long V_2A_2 and A_1A_2 intervals at the left hand limbs of these two curves In part *B* after the administration of procainamide, ventricular echoes could be induced at V_1V_2 intervals between 300 and 440 msec (an increase in the echo zone to 140 msec) The curves of V_2A_2 and A_1A_2 intervals were shifted upward as a result of further slowing of the retrograde conduction of premature V_2 The V_2A_2 conduction interval of the earliest effective V_2 for example increased from the control of 360 msec to 390 msec after procainamide The V_2A_e curve was accordingly displaced upward

The results of all 12 experiments are summarized in Table I In eight dogs in Group I in which no ventricular echo occurred in the control state, the administration of procainamide led to the appearance of ventricular echoes in five dogs with

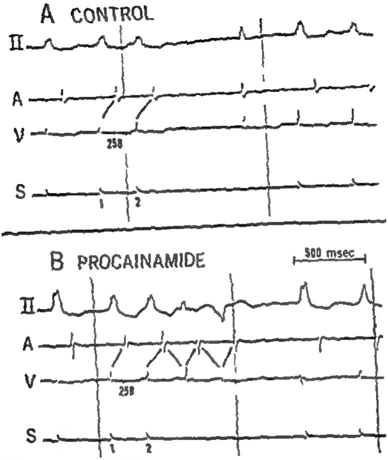

Fig 5 Development of a short run of ventricular reciprocal beats after the administration of procainamide Conventions as in Fig 1 See text for detailed description

the mean echo zone of 29 3 msec for the group In 12 dogs in Group II ventricular reciprocal beats were present in the control state with the mean echo zone of 38 3 msec In 10 of the 12 dogs the echo zone increased resulting into an increase in the mean echo zone to 67 8 msec for the group It should be noted that A V nodal reciprocation was often sustained and short runs of supraventricular tachycardia resulted in [illegible] of all 20 dogs *after* the administration of procainamide Fig 5 shows an example of sustained A V nodal reciprocation In the control state in panel *A* no ventricular reciprocal beats were induced by an early premature beat at a V V_2 interval of 258 msec In *panel B* after the administration of procainamide the premature V_2 at the same V V_2 interval *propagated* to the atrium more slowly (as indicated by a slightly longer V_2A_2 *interval than the control*) and was followed by repetitive reciprocal beats in the ventricle

Discussion

Many examples of reciprocal beats of the ventricle have been observed in clinical electrocardiography[6,7] Characteristically a ventricular premature beat is propagated retrogradely to the atrium and returns to the ventricle as an echo or *reciprocal beat* *Reciprocal* atrial beats have also been *observed* less frequently as atrial premature *beats* return to the atrium as echoes[6] The occurrence of these reciprocal *beats* has been shown to be due to functional longitudinal dissociation *of the A V node* into dual pathways[1,5] Such longitudinal dissociation is assumed to be a result *of the* disparity of refractory periods among different areas in the upper portion of the A V *node* *Basic* responses arriving at the A V node when all pathways of the A V node are fully *excitable* will be expected to propagate through the entire A V node An early premature however may find only one pathway excitable to transmit an

impulse and the other pathway would then be available for a return trip to the chamber of origin as an echo [1,3] An early premature beat, either ventricular or atrial is, therefore one of the conditions which expose dual A V nodal path ways and induce A V nodal reciprocation The perpetuation of such A V nodal reciprocation is believed to be responsible for many clinical cases of supraventricular tachycardia [4,5]

In the course of A V nodal reciprocation induced by an early premature response, the premature impulse must propagate slowly to the atrium through one area (α pathway) while it fails to excite other refractory areas (β pathway) of the A V node Additional time is then allowed for recovery of β pathway, which can then be invaded from the atrial margin for a return trip to the ventricle [1] Some portions of the A V conduc tion system must of course be activated twice, i e once during the retrograde conduction and again by the returning impulse This common pathway has been shown to be in the lower A V node and the His bundle [3] The necessity of a prolonged retrograde conduction through α path way is apparent If the retrograde conduction is too brief the returning impulse will arrive at β pathway and the common pathway during their refractory periods and no reciprocal beat will result In the heart in which ventricular recip rocal beats can be induced there is an echo zone or a range of the coupling intervals of ventricular premature beats (V_1V_2 intervals) within which sufficiently slow retrograde conduc tion is followed by a ventricular reciprocal beat [2] It has been shown that the echo zone can be widened by vagal stimulation which is known to slow conduction through the A V node [2]

Procainamide one of the frequently used agents against ventricular premature beats is known to increase refractory periods and decrease conduction rates of cardiac tissues including the A V node The drug may, therefore increase refractory periods nonuniformly in different areas of the A V node resulting in an increase in the disparity of refractory periods in the A V node and the increased likelihood of longitudinal disso ciation into α and β pathways Procainamide may also facilitate the development of reciprocal beats by increasing the retrograde conduction time through α pathway In the present study, ventric ular premature beats were propagated more slow ly and ventricular reciprocal beats were more frequently induced after the administration of procainamide Ventricular reciprocal beats oc curred after the administration of procainamide in many dogs in which no such echoes could be induced in the control state The drug also increased the echo zone significantly in most of the dogs in which ventricular echoes occurred before the drug administration No supraventric ular tachycardia could be induced in all dogs before the administration of procainamide but it developed in several dogs after the drug adminis tration These results demonstrated potentially deleterious effects of procainamide in facilitating the induction of A V nodal reciprocation by closely coupled ventricular premature beats

Summary

Procainamide is known to depress conduction through the A V node and this property may facilitate the development of ventricular recip rocal beats or echoes The occurrence of ventric ular reciprocal beats was studied in 20 open chest dogs before and after the administration of pro cainamide While the ventricle was paced by basic stimuli, early ventricular premature beats were introduced at various coupling intervals to induce ventricular echoes When ventricular echoes could be induced in a given heart there was a continuous range of coupling intervals (or echo zone) within which ventricular echoes occurred In the control state no echo occurred in eight dogs and the echoes developed in 12 dogs with the mean echo zone of 38 3 msec The effect of pro cainamide was studied at its therapeutic blood levels about 25 minutes after an intravenous injection of the drug in a dose of 10 mg per kilogram Of the first group of eight dogs in which no echo occurred in the control state four dogs developed ventricular echoes after the adminis tration of procainamide with the mean echo zone of 29 3 msec for the group Of the second group of 12 dogs in which ventricular echoes were induced in the control state the administration of pro cainamide increased the echo zone in 10 dogs with the mean echo zone of 67 8 msec for the group Ventricular reciprocal beats were often sustained to produce short runs of supraventricular tachy cardia in five dogs after the administration of procainamide The results demonstrated a poten tially deleterious effect of procainamide in facili tating the induction of A V nodal reciprocation by closely coupled ventricular premature beats

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Procainamide is known to depress conduction through the A V node and this property may facilitate the development of ventricular reciprocal beats or echoes The occurrence of ventricular reciprocal beats was studied in 20 open chest dogs before and after the administration of procainamide While the ventricle was paced by basic stimuli, early ventricular premature beats were introduced at various coupling intervals to induce ventricular echoes When ventricular echoes could be induced in a given heart there was a continuous range of coupling intervals (or echo zone) within which ventricular echoes occurred In the control state no echo occurred in eight dogs and the echoes developed in 12 dogs with the mean echo zone of 38 3 msec The effect of procainamide was studied at its therapeutic blood levels about 25 minutes after an intravenous injection of the drug in a dose of 10 mg per kilogram Of the first group of eight dogs in which no echo occurred in the control state four dogs developed ventricular echoes after the administration of procainamide with the mean echo zone of 29 3 msec for the group Of the second group of 12 dogs in which ventricular echoes were induced in the control state the administration of procainamide increased the echo zone in 10 dogs with the mean echo zone of 67 8 msec for the group Ventricular reciprocal beats were often sustained to produce short runs of supraventricular tachycardia in five dogs after the administration of procainamide The results demonstrated a potentially deleterious effect of procainamide in facilitating the induction of A V nodal reciprocation by closely coupled ventricular premature beats

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Self-anchoring electrode for implantable pacemakers

Orestes Fiandra
Walter Espasandín
Francisco Fernandez Barbieri
Mario Tornaria
Luis Peña Umpierrez
Hector Fiandra
Daniel Fiandra
Montevideo Uruguay

Permanent cardiac stimulation by means of intracavitary electrodes has almost universally displaced epicardial stimulation Ever since Furman and Schwedel [19] in 1959, showed that it is possible to keep the heart stimulated permanently by intracavitary electrodes, the latter have been progressively improved and increasingly used by investigators Nevertheless, each procedure still has its advantages and drawbacks [33] The anchorage of epicardial electrodes is surer but their implantation requires an aggressive surgical procedure, especially if it is taken into account that patients are generally elderly Intracardial electrodes are inserted by means of a procedure that is not very traumatic and the pacemaker may be implanted through the same incision by which the cephalic vein is exposed Their greatest drawback[35] is the shifting of the electrode which occurs in 3 1 to 44 per cent of implants [5, 6, 11, 14, 16, 17, 21, [illegible], 25, 28, [illegible], 33, [illegible], 40, 42, 44, 45, 48, 54, 57, 59, 60] Such shifting may occur early as well as late [41] up to 22 months[24] after implantation Migration of the electrode in general causes partial interruption[41] or cessation of stimulation In the latter case, it may have fatal consequences The seriousness of this complication has impelled some investigators[3, 65] to perform implantation in two stages in the first, they place the electrode in position and several days later if it has not shifted they connect it to the pacemaker

Shifting of intracavitary electrodes may occur for various reasons incorrect placement, pull on the catheter due to twisting of the pacemaker,[1] rejection by a mobile ventricle or lack of anchoring elements in excessively distended ventricles The catheter is pulled back when the pacemaker moves down in the pocket by its own weight and pulls the electrode that surrounds it This drawback is overcome by fastening the electrode to the neighboring tissue with nonextensible plastic sutures [8] such as Mersilene or by cementing it with silicone rubber adhesive to a patch of Dacron sewn to the pectoral [54]

Electrodes which have been correctly positioned and adequately anchored may shift if contraction to the heart is vigorous or if the trabeculations of the inside wall of the right ventricle are not very pronounced Under these circumstances migration may be an inevitable complication with ordinary electrodes requiring the physician to resort to thoracotomy to implant epimyocardial electrodes [35]

To overcome the serious and occasionally fatal drawback of migration, we have designed an electrode that we call self anchoring [15] which we have been using for the last 36 months

Material and methods

The self anchoring electrode consists of a wire of Elgiloy rolled in a spiral and insulated with a shield of silicone rubber The distal end is the really novel part of the electrode It is made of a

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Reprint request Orestes Fiandra Instituto Nacional de Cirugía Cardíaca Luis A De Herrera 2275 P O Box 954 Montevideo Uruguay

platinum cylinder 2 5 mm in diameter covered with silicone rubber to 1 mm from its distal end (Fig 1) The base is covered by an insulating layer of Elastometer which is electrically inert and very well tolerated by the tissues * By introducing a drift pin* inside the electrode and exerting pressure on it two platinum blades 3 7 mm long by 1 mm. wide and 0 1 mm thick (Figs 1 and 2) are spread out If the pin is withdrawn these blades remain in position perpendicular to the major axis of the electrode Because of their thickness they are solid but not traumatic If it is necessary to reintroduce them inside the cylinder to make a change in position of the electrode within the heart or to remove it completely if necessary another pin † constructed especially for the purpose need merely be inserted to the end of the catheter with exertion of gentle pressure and rotation of 180 degrees on its axis then withdrawing it several millimeters until the platinum blades are no longer visible A further turn of 180 degrees frees the pin which may be withdrawn from the electrode These operations may be repeated indefinitely Once the catheter is in final position the pin should be completely removed as it may cause rupture of the wire

We decided to make our electrode entirely of platinum although this is a precious metal and high in cost it is unalterable and practically not polarizable Connection of the platinum electrode with the wire is made by pressure with no welds thereby avoiding the drawbacks of the latter

The outer surface area of the electrode is 23 sq mm The first four electrodes were larger in surface area (38 sq mm)

To implant the self anchoring electrode the same routines that have been set up for ordinary intracavitary catheters are followed[1] After the electrode is in correct position the pin is removed and the threshold of stimulation is determined Although the values of this threshold vary broadly under physiologic conditions we have taken 5 microjoules (μJ) as an acceptable maximum value We determine the threshold by a technique affording maximum precision The microjoule is the most constant and useful measurement because it encompasses the fundamental parameters of the current of stimulation Only in cases in which we were unable after several attempts to obtain a lower threshold did we implant electrodes with thresholds higher than 5 μJ

*This drift pin is   of stainless steel wire, 0.35 mm. in diameter
†The point of this pin is a sm   hook that   tches the blades

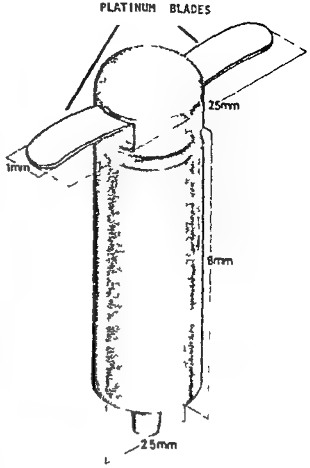

Fig 1 Distal end of self anchoring electrode

Results

After confirming experimentally that the self anchoring electrode was well tolerated by the right ventricle we performed implants in 63 patients between November 1971 and November 1974 (Table I) The ages of these patients at the time of implantation ranged from 45 to 86 years 38 of them are males

In no case did any complications appear

No self anchoring electrode migrated despite the fact that in nine cases (Cases 5 7 9 13 15 16 22 and 23) this electrode was used because of migration of a previously implanted ordinary electrode In two cases (Nos 6 and 13) migration occurred on two occasions In Case 17 it was impossible to implant a bipolar electrode because

Table 1 Thresholds obtained with recently implanted self anchoring electrodes

	Patient	Sex	Age	Threshold when implant				Second det of threshold (μJ)	Months
				(μJ)	V	mA	msec		
1	F H	M	76	06	05	1	12		
2	J M N	M	81	23	13	15	12		
3	F S	M	72	325	09	2	18		
4	S Z de S	F	61	18	07	15	18		
5	A M de P	F	58	035	025	05	28	254	16
6	B C de B	F	75	054	03	1	18		
7	F F de Z	F	45	072	09	26	15		
8	J S	M	80	117	06	15	13	4	17
9	R G S	F	69	075	05	1	15	76	15
10	F P de C	F	81	1	07	075	2		
11	V V de D M	F	70	098	05	13	15	4	15
12	F M P	M	70	123	05	13	19	54	15
13	J D D	M	71	19	07	16	17	5	12 2.16 15
14	P F	M	74	067	05	07	19		
15	A B de T	F	75	076	04	1	19		
16	D A U	M	84	17	08	12	18	3	21
17	N T	M	7[illegible]	051	04	07	18		
18	A C de C	F	66	36	1	2	18		
19	A M	M	72	11	045	15	16		
20	J C P	M	86	056	04	1	14		
21	J J Z L	M	71	036	06	12	05		
22	M H F	F	60	14	05	15	18		
23	A R	M	65	12	1	3	08	16	10
24	A I T	M	70	198	11	18	1		
25	L G	M	73	06	05	15	08		
26	B R de P	F	59	049	07	07	1		
27	P B	M	82	134	28	6	08		
28	A R	M	69	084	07	15	08		
29	J C R	M	79	04	05	1	08		
30	F G C	M	67	036	06	06	12		
31	E C de L	F	57	05	05	1	1		
32	E M de M	F	72	04	0.5	1	08		
33	J A R	M	82	032	04	09	09		
34	J P G M	M	58	125	14	1	09		
25	O G M de C	F	60	11	08	16	09		
36	C C de S	F	82	054	06	1	09		
37	B C	M	72	1	12	15	06		
38	N M	M	68	09	05	18	1		
39	A W	M	82	078	06	13	1		
40	F S	M	67	04	04	1	1		
41	R R	M	70	05	05	1	1		
42	E R	M	50	054	06	1	09		
43	E M de G	F	77	014	03	05	09		
44	L C	M	72	12	12	1	12		
45	F C de I	F	57	025	04	07	09		
46	R V de G	F	71	27	17	2	08		
47	J T	M	72	044	07	07	09		
48	Z W de M	F	51	043	06	08	09		
49	J P	M	60	028	05	07	08		
50	S B	M	81	013	03	05	09		
51	M C	M	45	03	05	1	07		
52	S T de S	F		12	12	1	1		
53	A N	M		035	05	07	1		
54	C M de B	F	72	06	05	12	1		

Table I cont d

	Patient	Sex	Age	Threshold when implant (μJ)	V	mA	m ec	Second det of threshold (μJ)	Months
55	M S de D	F	63	0 87	0 8	1 2	0 9		
56	O I	M	48	0 64	0 8	0.8	1		
57	E C	M		1	1	1	1		
58	N U	M	61	0 42	0 6	0 7	1		
59	E T S	M	80	0 15	0 5	0 3	1		
60	H S de N	F	45	0 75	0 45	1	1		
61	E L	F	72	0 19	0 3	0 7	0 9		
62	J M de V	F	78	3 22	1 4	2.3	1		
63	C L	M	78	0 72	0 6	1 2	0 1		

Fig 2 Distal end of self anchoring electrode with blades retracted (*A*) and extended (*B*)

Fig 3 X ray front (*A*) and side (*B*) of patient with self anchoring electrode

it was rejected by the ventricle Only the self anchoring electrode remained in correct position In *Case 10* the self anchoring electrode was also rejected during the procedure but remained anchored once the blades were projected It should be pointed out that the study was conducted in a very unfavorable group of patients inasmuch as in 11 of them ordinary electrodes migrated—twice in two cases Only the self anchoring electrodes were successful This fact gives the study performed special value

The threshold of stimulation did not differ from those obtained with other electrodes [13] In Cases 7 13 and 23 the implantation threshold of

Table I Thresholds obtained with recently implanted self anchoring electrodes

	Patient	Sex	Age	Threshold when implant				Second det of threshold (μJ)	Months
				(μJ)	V	mA	msec		
1	F B	M	76	06	05	1	12		
2	J M N	M	81	23	13	15	12		
3	F S	M	72	325	09	2	18		
4	S Z de S	F	61	18	07	15	18		
5	A M de P	F	59	035	025	05	28	2 54	16
6	M C de B	F	75	054	03	1	18		
7	F F de Z	F	45	072	09	26	15		
8	J S	M	80	117	06	15	13	4	17
9	R G S	F	49	075	05	1	15	76	15
10	F P de G	F	81	1	07	075	2		
11	V V de D M	F	70	098	05	13	15	4	15
12	F M P	M	70	123	05	13	19	54	15
13	J D D	M	71	19	07	16	17	5	12 2 16 15
14	P F	M	74	067	05	07	19		
15	A B de T	F	75	076	04	1	19		
16	D A U	M	84	17	08	12	18	3	21
17	N T	M	75	051	04	07	18		
18	A C de G	F	66	36	1	2	18		
19	A M	M	72	11	045	15	16		
20	J C I	M	86	056	04	1	14		
21	J J Z L	M	71	036	06	12	05		
22	M H F	F	60	14	05	15	18		
23	A R	M	65	12	1	3	08	16	10
24	A F T	M	70	198	11	18	1		
25	L C	M	73	06	05	15	08		
26	[illegible] R de I	F	59	049	07	07	1		
27	P B	M	82	134	28	6	08		
28	A R	M	69	084	07	15	08		
29	J C R	M	79	04	05	1	08		
30	E G C	M	67	036	06	05	12		
31	[illegible] C de L	F	57	05	05	1	1		
32	E M de M	F	72	04	05	1	08		
33	J A R	M	82	032	04	09	09		
34	J P G M	M	58	125	14	1	09		
25	O G M de C	F	60	11	08	15	09		
36	C C de S	F	82	054	06	1	09		
37	B C	M	72	1	12	15	06		
38	N M	M	68	09	05	18	1		
39	A W	M	82	078	06	13	1		
40	F S	M	67	04	04	1	1		
41	R R	M	70	05	05	1	1		
42	E R	M	50	054	06	1	09		
43	E M de G	F	77	014	03	05	09		
44	L C	M	72	12	12	1	12		
45	F C de P	F	57	025	04	07	09		
46	R V de G	F	71	27	17	2	08		
47	J T	M	72	044	07	07	09		
48	Z W de M	F	51	043	06	08	09		
49	J P	M	60	028	05	07	08		
50	S B	M	81	013	03	05	09		
51	M C	M	45	03	05	1	07		
52	S T de S	F		12	12	1	1		
53	A N	M		035	05	07	1		
54	C M de B	F	72	06	05	12	1		

Table I cont d

Patient		Sex	Age	Threshold when implant				Second det of threshold (μJ)	Months
				(μJ)	V	mA	msec		
55	M S de D	F	63	087	08	12	09		
56	O I	M	48	064	08	08	1		
57	E C	M		1	1	1	1		
58	N U	M	61	042	06	07	1		
59	E T S	M	80	015	05	03	1		
60	H S de N	F	75	075	0 5	1	1		
61	E L.	F	72	019	03	07	09		
62	J M de V	F	78	322	14	23	1		
63	C L.	M	78	072	06	12	01		

Fig 2 Distal end of self anchoring electrode with blades retracted (*A*) and extended (*B*)

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it was rejected by the ventricle Only the self anchoring electrode remained in correct position In Case 10 the self anchoring electrode was also rejected during the procedure but remained anchored once the blades were projected It should be pointed out that the study was conducted in a very unfavorable group of patients inasmuch as in 11 of them ordinary electrodes migrated—twice in two cases Only the self anchoring electrodes were successful This fact gives the study performed special value

The threshold of stimulation did not differ from those obtained with other electrodes[11] In Cases 7 13 and 23 the implantation threshold of

the self anchoring electrode was lower than that of the previous electrode at the time of its implantation, in Case 6 it was the same, and in Case 22 it was slightly higher (1 35 and 1 4 μJ, respectively)

Discussion

We may conclude from the experience described that (1) the self anchoring electrode very satisfactorily resolves the dangerous problem of migration (2) its electrophysiologic behavior does not differ from that of ordinary electrodes that are considered satisfactory, (3) its use presents no complications

Several not very effective attempts have been made to create electrodes that will not migrate Some pacemaker manufacturers (Medtronic Cordis General Electric) have put a little ridge of silicone rubber at the back of the electrode in an attempt to facilitate their anchorage If this device were really effective it would be dangerous, because if endocarditis were to put in an appearance it could not be removed, thus creating a serious complication

Other electrodes that send out 4 nylon filaments have been manufactured These nonconducting filaments have the drawback that they may perforate the ventricular wall or separate the electrode from the endocardium, thus losing the good contact required for proper stimulation Among 80 patients[9] four presented this problem, three cases of exit block 3 weeks after implantation

Udall[42 43] and Bleifeld and associates[4] have experimented with short term use of electrodes provided with hooks for attachment to the ventricular wall Wende and Schaldach[47 48] in 1970 used a hook electrode in three human subjects but made no comments on the progress of these patients Nor did they publish any subsequent study Apparently the use of this electrode was not free of risks [4] In addition, it is to be noted that the steel hooks used may cause microtraumatisms capable of causing bleeding and thrombosis in the vicinity of the electrode [47]

Rosenkranz and Schaldach[32] have created an electrode with hooks that is intended to be anchored in the atrial tissue It cannot be compared with ours in either action or intent

Summary

The writers describe a self anchoring monopolar electrode for use in implantable pacemakers, intended to prevent migration The device was implanted in 63 patients observed for 36 months and results are considered very favorable

We wish to thank Mr Mario J Risso for his assistance in construction of the self anchoring electrode

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The effects of acetylstrophanthidin on the response of the AV junction to adrenergic stimulation studied in dogs

Gerald A. Porlier, M.Sc.*
Victor Elharrar, Ph.D.
Pierre Gauthier, Ph.D.*
Réginald A. Nadeau, M.D.**
Montreal, Québec, Canada

The effects of digitalis glycosides on pacemaker sites and on AV conduction pathways are well documented. Their mechanisms of action remain, however, a matter of active research and controversy. Activation of peripheral reflexogenic areas,[1] central vagal stimulation, ganglionic transmission facilitation, and enhanced excitability of peripheral nerve endings have all been demonstrated. An antiadrenergic action at the heart level has also been proposed.

The present series of experiments were designed to assess the effects of acetylstrophanthidin on the response of the AV junctional tissues to adrenergic stimulation. Injection of acetylstrophanthidin directly into the AV node artery permits a selective action of this substance on the AV junction, avoiding those on other sensitive areas of the heart and on peripheral reflexogenic areas. The responsiveness of the AV junction to electrical sympathetic stimulation and to catecholamines injected into the AV node artery was evaluated before and at various times after intranodal injection of acetylstrophanthidin.

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* ll w f the Canadia Heart F nd tio

** Associat f th Medical Rese rch Cou cil f Canad

Methods

Thirty-five mongrel dogs weighing 10 to 20 kilograms were anesthetized with sodium pentobarbital (30 mg. per kilogram intravenously). Respiration was maintained with a cuffed endotracheal cannula connected to a Harvard pump. The thorax was opened at the level of the fourth intercostal space and the heart cradled in the pericardium. The sinus and AV node arteries were dissected free at their origin and cannulated. Heparin (3 mg. per kilogram intravenously) was administered before completion of cannulation. The responsiveness of each preparation was ascertained by injecting acetylcholine into the AV node artery. Only dogs responding by complete AV block to a concentration of 1 μg or less of acetylcholine were retained for further study.

In 11 dogs, the left stellate ganglion was exposed and decentralized and the cardiac branch was stimulated through bipolar silver electrodes. Square wave stimuli of supramaximal voltage and of 2 msec. duration were delivered by an S4 Grass stimulator during 20 seconds at 3, 10, and 30 Hz. This group received 20 μg of propranolol into the sinus node artery in order to prevent sinus acceleration from left stellate ganglion stimulation. Norepinephrine (9 dogs) and isoproterenol (8 dogs) were injected into the AV node artery at concentrations of 0.1, 1.0, and 10.0 μg. Acetylstrophanthidin (5 μg) was injected into the AV node artery of dogs which responded to adrenergic stimulation by the emergence and acceleration of an AV junctional rhythm.

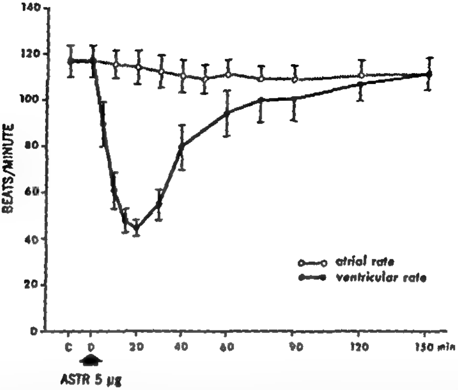


Fig 1 Effects of acetylstrophanthidin on atrial rate (broken line) and ventricular rate (full line) in 14 dogs following the injection of 5 µg of acetylstrophanthidin into the AV node artery A minimum ventricular rate of about one third of the atrial rate was reached within 20 minutes when the heart was in complete AV block As AV conduction recovered the ventricular rate returned gradually toward its initial value which was attained between 75 and 120 minutes after the injection of acetylstrophanthidin

Table I Principal effects of acetylstrophanthidin (5 0 µg), on the AV junctional tissues

Total no of dogs	No of dogs having presented			
	First degree AV block	Second degree AV block	Complete AV block	Decrease in ventricular rate
28	4	7	14	3*

*These three dogs were in atrial fibrillation before the injection of acetylstrophanthidin into the AV node artery

In three dogs atrial fibrillation was induced faradically by high frequency stimulation through bipolar electrodes fixed to the free wall of the right atria

The following electrical tracings were recorded ECG (lead aV_R) and atrial and ventricular electrograms, the latter two obtained through bipolar pin electrodes fixed to epicardial surfaces Arterial blood pressure was monitored by a Statham strain gauge (P23Dc) from a polyethylene cannula inserted into the left femoral artery Electrical and blood pressure tracings were recorded with an ink writing Grass polygraph (model 7) at a paper speed of 25 mm per second for heart rate determination and 100 mm per second for measurement of the PR interval duration

The following drugs were used acetylstrophanthidin (Eli Lilly) acetylcholine chloride (Sigma Chemical) isoproterenol HCl (Winthrop Laboratories), *l* arterenol D bitartrate monohydrate (Mann Research Laboratories) and propranolol (Ayerst Laboratories) All drugs were dissolved in fresh Ringer s solution Injections into the AV node artery were made with a 1 0 ml hand driven syringe and were completed within 30 seconds When increasing concentrations were administered serially, the heart rate was allowed to return to its preinjection value for at least 2 minutes before the next injection Following each injection the cannula was rinsed with 1 0 ml of Ringer s solution

Results

Effects of acetylstrophanthidin *injected into* **the AV node artery** The effects of acetylstrophanthidin (5 µg) injected directly into the AV node artery were observed in 28 dogs and are summarized in Table I In four dogs only a first

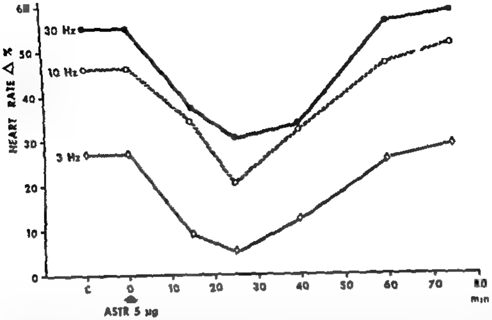


Fig 2 Response of the AV junction to left stellate stimulation before and after the injection of acetylstrophanthidin (5 µg) into the AV node artery Control left stellate stimulation elicited an AV junctional acceleration of 27 45 and [illegible] per cent at 3 10 and 30 Hz respectively Fifteen minutes after the injection the AV junction response was almost abolished at 3 Hz and remained inhibited until 45 minutes The AV junctional response to 10 and 30 Hz reached a minimum of 21 and 30 per cent 25 minutes after the injection This response returned gradually and a response identical to control was obtained at all frequencies of stimulation 75 minutes after the injection of acetylstrophanthidin

degree AV block was noted whereas in others the PR interval increase was followed by more marked degrees of AV block Wenckebach cycles and second degree AV block were seen in 21 dogs and were succeeded by a complete AV block in 14 Progression to complete AV block occurred without modification of the QRS morphology in 10 dogs whereas aberrant QRS complexes appeared in four others These effects are similar to those described in previous publications from this laboratory

The progressive impairment of AV conduction resulted in a decrease of the ventricular rate This is illustrated in Fig 1 where the atrial and ventricular rates are plotted as a function of time elapsed since acetylstrophanthidin administration These results were obtained in 14 dogs which responded to acetylstrophanthidin by a complete AV block While the atrial rate remained unchanged the ventricular rate decreased and attained a minimum of about one third of the atrial rate within 20 minutes at a time when the heart was in complete AV block The ventricular rate then gradually returned to its initial value between 75 and 120 minutes after the injection of acetylstrophanthidin

In three dogs in atrial fibrillation a decrease of the mean ventricular rate was observed following injection of acetylstrophanthidin (5 µg) into the AV node artery Mean ventricular rate decreased from 139 ± 7 (mean ± S E M) to 91 ± [illegible] beats per minute

Effects of acetylstrophanthidin on the AV junction response to adrenergic stimulation Upon adrenergic stimulation of the AV junction an AV junctional rhythm of a rate higher than the sinus rhythm took over the control of the heart The control chronotropic response of the AV junction to left stellate ganglion stimulation and to intranodal injection of various concentrations of norepinephrine and isoproterenol are summarized in Table II These responses were frequency and dose related and were similar whatever the mode of adrenergic stimulation used In these experiments AV junctional rhythm was defined from the ECG tracing when the normal or inverted P wave fused with or was closely coupled with (or followed) the QRS complex the latter remaining unchanged

Acetylstrophanthidin significantly reduced the chronotropic response of the AV junction to adrenergic stimulation When a first degree AV

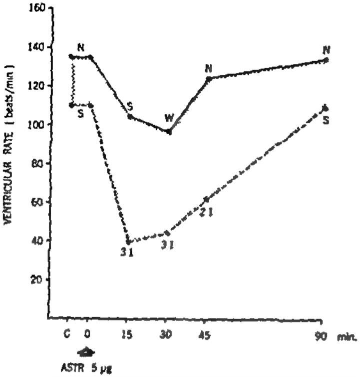


Fig 3 Response of the AV junction to isoproterenol (1 0 μg) before and after the injection of acetylstrophanthidin (5 0 μg) into the AV node artery The broken line represents the ventricular rate just before the injection of isoproterenol into the AV node artery The solid line represents the maximum ventricular rate obtained after the injection of isoproterenol The shaded area represents the corresponding ventricular acceleration Control intranodal injection of isoproterenol elicited an AV junctional rhythm at a rate of 135 b p m Fifteen minutes after the injection of glycoside the heart was in 3 1 AV block At this time isoproterenol reduced the block from 3 1 to 1 1 conduction at 30 minutes only Wenckebach cycles could be obtained Thereafter the AV junctional response to isoproterenol returned gradually with the recovery of AV conduction A response identical to control was observed when normal conduction was restored 90 minutes after the injection of acetylstrophanthidin *S* Sinus rhythm *N* AV junctional rhythm *W* Wenckebach cycles

block was the main effect of acetylstrophanthidin (four dogs) the chronotropic response of the AV junction to left stellate ganglion stimulation (two dogs) was decreased at all frequencies tested (Fig 2) and reached a minimum approximately 20 minutes after the injection of acetylstrophanthidin A similar decrease in the AV junctional response to various concentrations of norepinephrine (one dog) and isoproterenol (one dog) was also observed These effects were reversible The chronotropic response gradually returned to control value as normal conduction was restored (Fig 2)

When a second degree AV block was the major effect of acetylstrophanthidin (seven dogs), left stellate stimulation (one dog) norepinephrine

Table II Chronotropic responses of AV junction to adrenergic stimulation before the injection of acetylstrophanthidin (5 0 μg), into the AV node artery

Type of adrenergic stimulations	*Mean heart rate ± S E (b p m)* Before	*Mean heart rate ± S E (b p m)* After	*Mean Δ AV junctional acceleration ± S E (b p m)*
Left stellate ganglion stimulation (N = 8)			
3 Hz	107 5 ± 7 3	123 86 ± 8 16	16 38 ± 4 7
10 Hz	107 25 ± 7 01	151 86 ± 7 97	44 63 ± 2 99
30 Hz	107 13 ± 7 25	159 5 ± 9 3	52 38 ± 4 16
Norepinephrine (N = 9)			
0 1 μg	120 44 ± 6 36	139 11 ± 7 73	18 67 ± 4 79
1 0 μg	120 56 ± 6 39	157 22 ± 8 38	36 67 ± 6 77
10 0 μg	120 33 ± 6 36	164 89 ± 8 83	44 56 ± 6 84
Isoproterenol (N = 8)			
0 1 μg	115 13 ± 7 71	141 26 ± 5 42	26 13 ± 5.24
1 0 μg	115 5 ± 7 57	160 75 ± 7 68	45 25 ± 7 91
10 0 μg	117 25 ± 6 95	189 88 ± 6 94	72 63 ± 7 43

(three dogs) or isoproterenol injections (three dogs) could no longer elicit a junctional rhythm but could however reduce the degree of AV block, as illustrated in Fig 3 For this reason the degree of adrenergic inhibition could not be assessed in a quantitative manner When complete AV block followed the injection of acetylstrophanthidin into the AV node artery (Fig 4) left stellate stimulation (five dogs) as well as norepinephrine (five dogs) and isoproterenol (four dogs) produced only a slight increase in AV junctional rate The effects of adrenergic stimulation returned gradually along with the recovery of AV conduction (Figs 3 and 4)

During atrial fibrillation, stimulation of the left stellate ganglion produced an increase of the mean ventricular rate of 121 ± [illegible] (S E M) b p m This increase was reduced by the injection of acetylstrophanthidin (5 μg) into the AV node artery A marked inhibition of about 80 per cent of the effect of left stellate ganglion stimulation

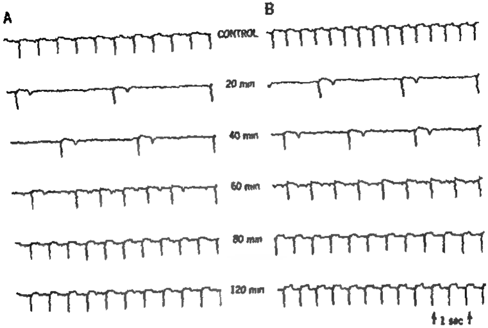


Fig 4 Response of the AV junction to the intranodal injection of 10 μg of norepinephrine at various times after acetylstrophanthidin (5 0 μg) into the AV node artery in one dog *Panel A* shows the ECG tracings before and at various times after the intranodal injection of acetylstrophanthidin *Panel B* shows the AV junctional response to norepinephrine in the same animal *Control* injection of norepinephrine elicited an AV junctional rhythm and tachycardia from 10([redacted] 148 b p m Twenty minutes after the injection of glycoside the heart was in complete AV block and norepinephrine at this time had no effect on the junctional rhythm but produced a slight acceleration (6 b p m) of the ventricles AV junctional response to norepinephrine returned gradually in time (40 60 and 80 minutes) in parallel with the AV conduction recovery A response identical to control was obtained after 120 minutes when AV conduction was completely restored

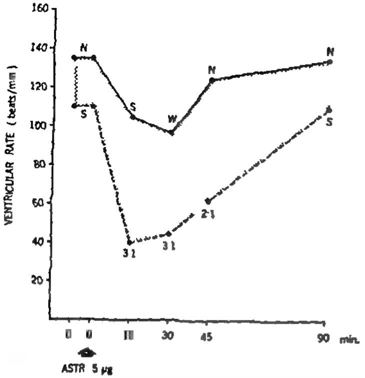
on the mean ventricular rate was observed in all three dogs 20 minutes after the injection of acetylstrophanthidin into the AV node artery One of these experiments is illustrated in Fig 5

Response of the AV junction to adrenergic stimulation during spontaneous AV block In the course of these experiments seven dogs spontaneously presented a 2 1 and two others a 3 1 AV block without the administration of acetylstrophanthidin The appearance of impaired conduction may have been related to ligation and cannulation of the AV node artery and to decentralization of the left stellate ganglion These animals served as controls in order to verify whether the inhibition of the AV junctional response to adrenergic stimulation was related to the action of acetylstrophanthidin or to the AV block per se The left stellate ganglion was stimulated in three dogs whereas norepinephrine or isoproterenol were injected into the AV node artery in four dogs.

Fig [redacted] illustrates the effects of left stellate stimulation on the AV junctional rhythm before and during the spontaneous AV block Before AV nodal artery cannulation the heart was in normal sinus rhythm at a rate of 122 b p m and left stellate stimulation (10 Hz) elicited an AV junctional rhythm at a rate of 150 b p m (Fig 6 *A*) Repetition of the stimulation during spontaneous 2 1 block brought about 1 1 rhythm followed rapidly by an AV junctional rhythm which accelerated to 152 b p m The 2 1 block was restored upon cessation of the stimulation (Fig 6 *B*) A similar response was obtained with injection of norepinephrine into the AV node artery, as can be seen in Fig 7 These results suggest that the inhibition of the AV junctional response to adrenergic stimulation is not related to the impaired AV conduction per se

Discussion

The AV junctional response to adrenergic stimulation is decreased after the injection of acetylstrophanthidin directly into the AV node artery of the dog These effects on the AV junction are similar to earlier reported observations



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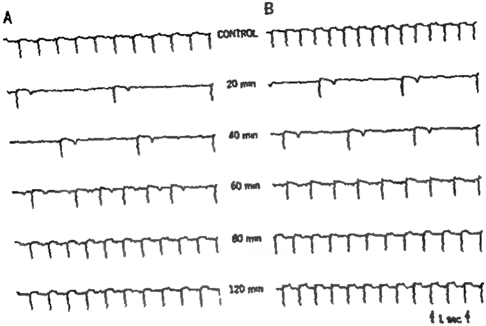

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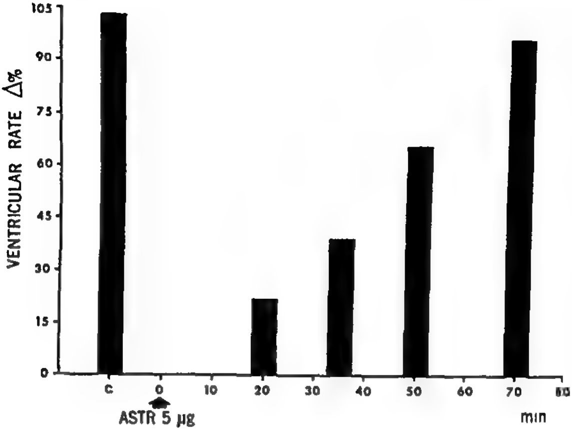

Fig 5 Effect of left stellate stimulation (30 Hz) on ventricular rate during atrial fibrillation before and after the injection of 5.0 μg of acetylstrophanthidin into the AV node artery observed in one dog Before the injection of glycoside left stellate stimulation caused an increase in ventricular rate of 104 per cent Repetition of sympathetic nerve stimulation 20 minutes after the injection of acetylstrophanthidin produced an increase in ventricular rate of only 22 per cent Thereafter the increase in ventricular rate gradually returned to control values

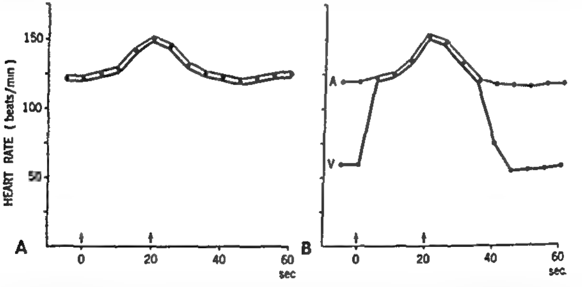

Fig 6 Response of AV junction to left stellate stimulation at 10 Hz before and after the establishment of a 2 1 AV block in a control animal Broken line represents atrial rate full line represents ventricular rate Left stellate stimulation for 20 seconds (between the arrows) while the heart was in sinus rhythm elicited an AV junctional rhythm which accelerated from 122 to 150 b p m (*A*) Repetition of the stimulation after the spontaneous establishment of a 2 1 rhythm produced a 1 1 rhythm followed rapidly by an AV junctional rhythm which accelerated to 152 b p m and was succeeded by a return to 2 1 rhythm (*B*)

on sympathetic inhibition by this substance at the level of the sinus node[11] These results further confirm the findings of Mendez and associates,[10] who reported a diminished sinus and AV nodal acceleration from norepinephrine and sympathetic stimulation following intravenous administration of acetyldigitoxin

It has been shown that digitalis induced bradycardia occurring in vagotomized or atropine pretreated animals was prevented either by

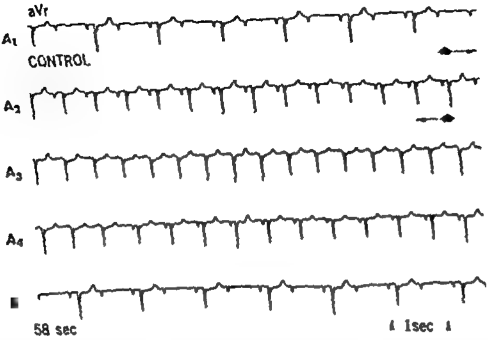

Fig 7 Response of the AV junction to norepinephrine after appearance of a spontaneous 2 1 AV block. During 2 1 AV block (*strip A*) the injection of 0 1 µg of norepinephrine (between the arrows) into the AV node artery elicited an almost instantaneous (less than 1 second) acceleration of the ventricles followed by a progressive shortening of the PR interval in 1 1 rhythm (*strip A*) *One second after the injection of norepinephrine* an AV junctional rhythm appeared which accelerated to 125 b p m with 1 1 retrograde AV conduction (*strip A*) succeeded by sinus rhythm (*strip A*) Return to 2 1 AV *rhythm occurred* 58 seconds after the norepinephrine injection (*strip B*) Strips A to A are continuous ECG tracings were obtained in Lead aVR at a paper speed of 25 *mm* per second

pretreatment with beta adrenergic blocking agents [20] or by total cardiac denervation [21] Inhibition of the positive inotropic action of norepinephrine by ouabain has also been reported in the dog and in isolated rabbit atrial preparations [2] A decreased chronotropic response to isoproterenol following ouabain administration has also been observed by others and was shown to be related to a beta receptor blocking effect Likewise Ten Eick and associates [7] demonstrated that the inhibiting effect of cardiac denervation on postcardioversion arrhythmias in dogs was increased by ouabain suggesting a beta blocking effect of ouabain

The possibility that the antiadrenergic effect of acetylstrophanthidin is the result of an antagonistic action between glycosides and catecholamines at the level of the Na K ATPase pump merits some attention Inhibition of the Na K ATPase activity by cardiac glycosides is a well known effect stimulation of this enzymatic system by catecholamines has recently been demonstrated on cardiac Purkinje fibers [26] Such an antagonism would explain the close relationship noted between the degree of inhibition of adrenergic effects on AV conduction and AV conduction defects produced by acetylstrophanthidin During complete AV block the inhibition of the NA K ATPase activity by acetylstrophanthidin would be less than its activation by catecholamines thus reducing only the chronotropic and dromotropic responses of the AV junctional tissues

AV conduction disorders varied from first degree to complete AV block and originated within the AV junctional tissues as indicated by the evolution of the atrial and ventricular rates following local injection of acetylstrophanthidin (Fig 1) It is interesting to note that during complete AV block the ventricular rate was approximately one third of the atrial rate Erlanger[3] was the first to report such a 3 1 ratio after mechanically induced complete AV block in dogs

Mendez and associates[11] have shown that acetyldigitoxin increased the AV junction functional refractory period only if the heart was under normal sympathetic influence or tone An

increased functional refractory period of the AV junction after ouabain has been shown to partially depend upon the integrity of the sympathetic innervation and/or the presence of a normal endogenous catecholamine content [12] The close relationship between the degree of AV conduction defects and the decreased responsiveness of the AV junction to adrenergic stimulation suggest that this antiadrenergic effect may be involved in the genesis of the AV conduction disturbances caused by digitalis intoxication This mechanism may also play a role in reducing the ventricular rate during atrial fibrillation

Summary

The response of the AV junction to adrenergic stimulation was studied in 35 anesthetized open chest dogs before and after the injection of acetyl strophanthidin (5 μg) directly into the AV node artery An AV junctional rhythm was obtained under control conditions by injecting norepinephrine (n = 9) or isoproterenol (n = 8) into the AV node artery and by stimulation of the left stellate ganglion (n = 11) after selectively injecting propranolol into the sinus node artery Acetyl strophanthidin brought about various degrees of conduction block from simple PR interval prolongation to complete heart block and decreased the chronotropic response of the AV junction to adrenergic stimulation In seven animals the appearance of a spontaneous second degree AV block did not reduce the AV junctional response to adrenergic stimulation Acetylstrophanthidin also reduced the ventricular acceleration produced by adrenergic stimulation during atrial fibrillation These results suggest that the antiadrenergic effect of cardiac glycosides may not only be involved in the mechanism of AV conduction disturbances during digitalis intoxication but may also play a role in slowing the ventricular rate during atrial fibrillation

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Endocardial changes produced in Patus monkeys by the ablation of cardiac lymphatics and the administration of a plantain diet

Brian McKinney, D Sc, M D, M R C Path
London England

Endomyocardial fibrosis (EMF) is a cardiomyopathy which occurs very frequently in many parts of the tropics such as Uganda,[1,2] Nigeria,[3] and Brazil[4] There have also been reports of EMF from temperate areas such as North America[5]

Although many of these cases are in Europeans who have lived for long periods in the tropics[6] some are in others who have spent shorter periods of time there but under prolonged conditions of dietary privation[7] The majority of the cases of EMF reported in temperate areas are however, in indigenous inhabitants of the tropics who have migrated to Europe[8]

Many cases commonly thought to be EMF, such as those from Ceylon[9] or Turkey[10] are in fact, cases of cardiomegaly of unknown origin (CUO) or adult fibroelastosis

The etiology of this disease is entirely unknown but it seems to have a particular geographic distribution in that it usually occurs only in areas where the indigenous populations, in whom this disease is found, use plantains as their only, or principal dietary staple It has been suggested by some workers[11] that this disease has an infectious origin and that the causative agent is a filaria the mechanism for the endocardial fibrosis being obstructions of cardiac lymphatic drainage by these parasites A specific cause due to filaria, as has been suggested by Ive and Brockington,[12] is unlikely as such parasites are widespread geographically whereas the tropical cardiomyopathies, and particularly EMF, usually have a restricted distribution[13]

A combination of obstruction of cardiac lymphatics and a plantain diet may be necessary the latter to prevent excessive elastic tissue formation in the endocardium apparently being due to the inhibitory action of 5 hydroxytryptamine (5 HT), of which plantain contains a large amount, on elastic tissue formation

This work has previously been attempted in dogs[14] but with no success Even in the animals which were used as controls only having their cardiac lymph supply ablated no endocardial fibrosis was produced It was thought that these results should be disregarded when it is appreciated how easily fibroelastic lesions of the endocardium have been produced by Miller Pick and Katz[15]

Methods

In order to obtain as accurate an experimental model as possible primates were used instead of dogs thereby removing a possible error in that this disease may be species specific no lesions similar to EMF having yet been reported in any wild or domestic animals Also because of the fact that EMF is usually found in adolescents or young adults the group most commonly affected being persons 15 to 25 years of age, young monkeys 6 to 8 months old were used being then kept alive for a further 2 years Eight Patus monkeys aged 6 to 8 months at the beginning of the study, were used

The first part of this study was to ablate the cardiac lymph supply of the animals used

The animal was anesthetized and a left sided thoracotomy was then performed A 1 ml solution of Evons Blue dye (T 1824) was then injected

From the Royal Free Hospital London England

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Reprint requests Dr Brian McKinney University Hospital of Wales Sully Hospital Sully Glamorgan CF6 2YA Wales

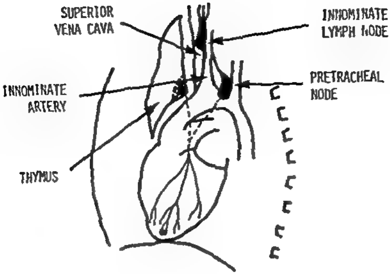

Fig 1 Diagram to show the distribution of lymphatics in the Patus monkey (Based on a diagram by Miller A. J., Pick, R and Katz, L. N Br Heart J 25 182 1963)

Table 1 Body weight and weights of internal organs in Patus monkeys

	Controls					*Plantain diet*				
	Individuals				*Mean*	*Individuals*				*Mean*
Body weight (Kg)	9 6	5 4	9 0	9 8	8 5	4 1	2 3	5 7	3 2	3 9
Heart weight (Gm)	70	34	51	84	60	26	19	33	[illegible]	24
Liver weight (Gm)	164	87	17[illegible]	1[illegible]0	136	101	80	103	84	92
Spleen weight (Gm)	17 1	5 5	7 5	5 7	8 9	4 4	3 6	5 1	3 2	4 1
Left kidney weight (Gm)	15 2	10 0	9 9	13 7	12[illegible]	7 2	6 1	8 7	6 3	[illegible] 1
Right kidney weight (Gm)	17 4	10 1	9 9	14 4	1[illegible]9	7 7	6 0	8 4	6 2	[illegible] 1

into the cardiac apex and after 2 to 3 minutes the cardiac lymphatics passing over the pericardium could be clearly localized It was found that most of these lymphatics drained directly into small groups of lymph glands at the base of the heart Some of these cardiac lymphatics drained into the left lobe of the thymus (Fig 1) Therefore to completely destroy cardiac lymph drainage the left lobe of the thymus was also resected The lung was then fully re-expanded and the chest closed without a drain Skin closure was achieved by subcuticular sutures and the wound was fully covered by Nobecutane The animal was then returned to its cage after a nerve block with local anesthetic of the three intercostal nerves most adjacent to the thoracotomy had been carried out to prevent postoperative pain Of the eight monkeys which had been operated on four animals were fed on a diet similar to that eaten by the indigenous inhabitants affected by EMF in Uganda—this consisting largely of cooked (steamed) plantains obtained from Uganda East Africa The other four animals received a normal diet consisting of Purina monkey chow ad libitum together with chopped carrots dates and cabbage twice a week While these animals were alive blood counts estimates of serum enzymes chest radiograms and electrocardiograms (ECG) were carried out

The diets were continued until the animals were eventually put to death

The following staining methods were used in the histologic examination of material obtained at autopsy from these animals (1) hematoxylin and eosin—for general morphology (2) Martius Scarlet Blue—for fibrin (3) Alcian Blue—for acid

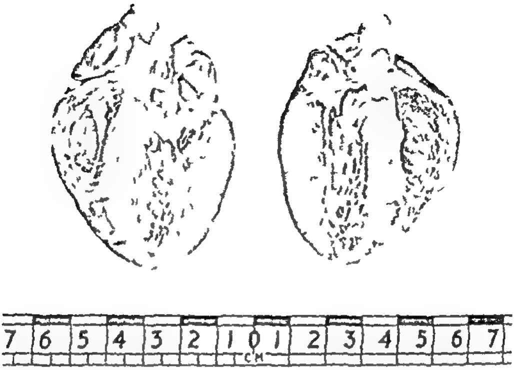

Fig 2 Monkey 9 showing the dull gray appearance of the endocardium of both atria and ventricles A few small areas of endocardial thickening are present

Table II Serum phosphokinase levels

	March 23 1968	*Dec 5 1968*	*March 10 1969*	*Mean*
Control				
8	71	116	70	85 7
[illegible]	28 5	110	120	86 2
10	40	82	70	64
13	40	69	50	53
Mean	44 9	94	77 5	72 2
Plantain				
7	157	102	65	10[illegible]
12	138	113	105	116
14		82	67	74 5
Mean	147	99	75 7	98 4

mucopolysaccharides and (4) Verhoef-Van Giesen and Orcein—for elastic tissue

Results

Weight The weights of the four monkeys on normal diets have remained within normal limits although they have all increased in weight as part of their normal growth pattern and at maturity these animals weighed between 5 4 and 9 8 kilograms (mean 8 46 kilograms)

The weights of the four monkeys on the plantain diet increased much more slowly and these animals finally weighed between 2 3 and 5 6 kilograms (mean 3 88 kilograms)

The final weight of these animals was 46 per cent of that of animals fed the normal control diet It could be considered that these animals were malnourished—the difference between the weights of these two groups of animals (controls and plantain fed) was statistically significant ($p < 0 01$ to $< 0 02$) The statistical significance in differences in mean value between the control and treated groups was assessed by a rank test These weights are all listed in Table I

Hematologic investigations These have proved that all these animals have normal values and that in none was an eosinophilia present

ECG studies These were carried out with a Nihon Kohden ECG while the animals were anesthetized 'Baby' electrodes were used but only three chest leads (V_1 V_2 and V) could be used owing to the animals small size The pattern of these ECG s was abnormal but inconclusive

Serum enzymes The following four enzymes were for about a year, studied in these animals creatine phosphokinase (CPK) hydroxybutyrate dehydrogenase glutamic oxalacetic transaminase and lactic dehydrogenase As can be seen in Table II, the serum levels of creatine phosphokinase were not significantly altered in any of these animals from their preoperative levels either by cardiac lymphatic obstruction alone or when associated with a plantain diet No serum CPK levels were estimated in one of the monkeys

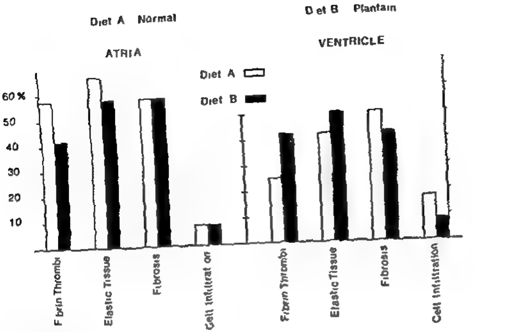

Fig 3 Histogram to demonstrate the changes found in the endocardium of monkeys which have been kept on normal or plantain diets

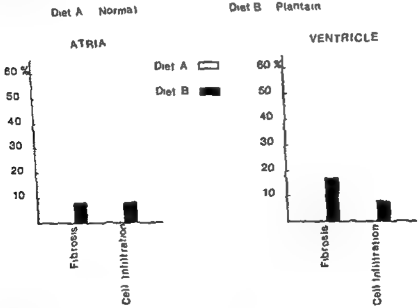

Fig 4 Histogram to demonstrate the changes found in the myocardium of monkeys which have been kept on normal or plantain diets

(M 15) on a plantain diet as it was technically impossible to obtain specimens of blood from this animal This part of the study was therefore discontinued after about a year

Pathologic findings at autopsy One of these animals (M 9) died about [illegible] months before the other animals were killed from a *B coli* septicemia The heart was not involved in this disease process and the cardiac changes will be described in conjunction with those of the other seven monkeys

The cardiac changes found at autopsy, in these

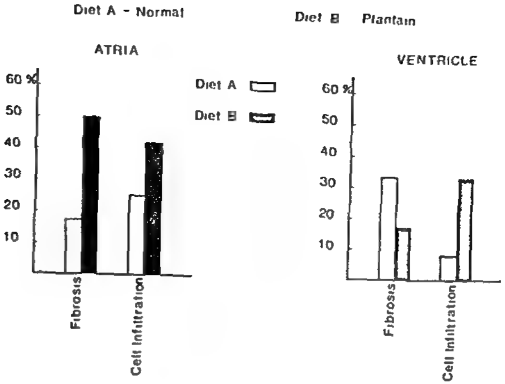

Fig 5 Histogram to demonstrate the changes found in the pericardium of monkeys which have been kept on *normal or plantain diets*

Fig 6 The endocardium of the left atrium in a monkey fed on a plantain diet in addition to cardiac lymphatic obstruction is in this case normal

animals were as follows A few scanty pleural adhesions were found in three animals these attaching the pericardium to the surrounding parietal and visceral pleura of the lower lobe of the left lung Externally the hearts of all the animals appeared normal except that all were dilated particularly the atria In those fed a plantain diet this was more marked and the hearts were smaller than in those on a normal diet

When the hearts were opened the endocardium, particularly that in the atria was gray and dull in appearance (Fig 2) having lost the transparent *and glistening appearance of the normal endocardium*

A few small areas of endocardial thickening were present and this was most intense at the *ventricular apices The myocardium was normal* In no parts of the cardiac cavities of any of these hearts were antemortem thrombi present or were small thrombi found which were adherent to the underlying endocardium

The results were graded 0 ± + or ++ signifying that a particular change was not found or was mild moderate or severe in degree The ± +, and ++ changes were given values of 1 2 or 3 The value of each factor is expressed as a percentage of the total value (12) which could be obtained The changes found histologically in the

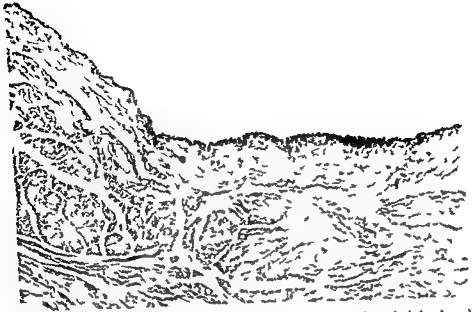

Fig 7 Slight fibrotic thickening of the endocardium in the ventricle of a monkey which has been kept on a plantain diet (Hematoxylin and eosin × 80)

Fig 8 Increased amount of elastic tissue in the thickened endocardium of a monkey which has been fed on a plantain diet. (Verhoef-Van Gieson × 80)

hearts of the monkeys are shown in Figs 3 4 and 5

The changes found in the hearts of the monkeys which had only had their cardiac lymphatics obliterated were largely the same as in those animals which had in addition subsisted on a plantain diet In monkey XI 9 which had only had its cardiac lymphatics ablated there was an infiltration often focal of the myocardium with lymphocytes and some polymorphonuclear cells This change was not thought to be important as the animal died from *B coli* septicemia

In monkeys fed on a plantain diet in addition to

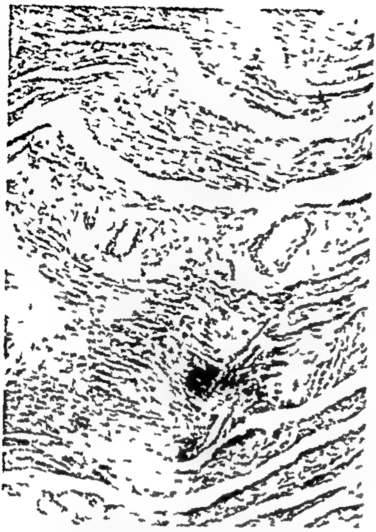

Fig 9 Intramyocardial blood vessels which are dilated and congested while surrounded by perivascular fibrosis (Hematoxylin and eosin × 80)

having their cardiac lymph supply ablated the endocardium was in most places normal, showing only a few endothelial cells and collagen fibers (Fig 6) This endocardial thickening was no more than in those animals which had only had their cardiac lymphatics ablated and had eaten a normal diet Sometimes a slight increase in fibrous tissue might be present and was most frequently seen on the ventricular side of the atrioventricular valves (Fig 7) Here the fibrous tissue might extend down for some distance into the myocardium so that a few of the muscle fibers were completely surrounded by fibrous tissue

There was sometimes, a slight infiltration of the endocardium with lymphocytes but this was not regarded as significant as this is commonly seen in hearts with a variety of other diseases and in normal hearts A thin layer of fibrin was sometimes found overlying the thickened endocardium A few larger deposits of fibrin were sometimes present in some parts of the endocardium, the most common location for them being the atrial endocardium Small deposits of fibrin were seen within the thickened endocardium although none of them appeared to be undergoing a process of organization to become part of the fibrous tissue of the thickened endocardium The endocardium contained an increased amount of elastic tissue (Fig 8) the fibers usually being long, unfragmented, and usually unbranched and untwisted The fibers were found in all parts of the endocardium but were less plentiful in the more superficial parts These elastic tissue fibers did not pass down into the underlying myocardium

The endocardium contained a normal amount of acid mucopolysaccharides

Sometimes the interstitial tissue of the myocardium was congested so that the myocardial fibers were separated by edema fluid, this change being seen in both groups of animals

There was no increase of interstitial tissue in the myocardium but sometimes a few small foci of fibrosis were seen although these were not very large The intramyocardial blood vessels were mostly normal although some were found to be congested and dilated Around these vessels there was very often an increase in perivascular fibrosis (Fig 9)

Nowhere in the myocardium was any lymphocytic infiltration to be seen except sometimes, in the subpericardial parts of the myocardium

All the myocardial cells were normal the cytoplasm of none being vacuolated or having lost their normal striation while all the nuclei were of normal size and shape and none were pyknotic

Discussion

These studies show that obstruction of the cardiac lymph supply will produce fibroelastic thickening of the endocardium It does not however when combined with feeding these animals a plantain diet produce EMF or even decrease the amount of elastic tissue fibers present

The reason for the small size of the hearts of the animals which were on a plantain diet is probably the simple one that they had existed for a long time on a low protein diet this having been shown previously in famine conditions [19]

The failure to produce marked endocardial

lesions in animals fed on a plantain diet is interesting when it is considered that this has been done in rats[17]

The most probable explanation for the failure to produce many severe endocardial lesions in these animals and the complete absence of lesions simulating EMF is probably related to the time scale and the need to initiate these dietary insults at a very early age

Vital organs are usually rigorously protected by the biologic system Thus Sinclair and Crawford[8] have shown that it is only possible to produce morphologic changes in the brain using low fat diets, over succeeding generations In these experiments a period of 20 months was required to produce symptoms of essential fatty acid deficiency in the capuchin monkey a much smaller primate than the Patus monkey In considering the relationship of these experiments to the production of EMF in Africa it is evident that the undernutrition necessary is not simply a matter of childhood marasmus or the poorly nourished adult but it is an exposure to malnutrition since conception

It is also now recognized that young adult animals if exposed to infection when malnourished will produce a much greater symptomatology than when well nourished

The damage from these infections on the myocardium should be easily reparable so that no traces remain when the cardiomyopathy is eventually well developed This event would then easily explain the supposition by some workers such as Parry and Abrahams[1] that there is always a history of infection before the clinical onset of EMF

Summary

The effect of obliteration of the cardiac lymph drainage and prolonged feeding with a plantain diet in Patus monkeys was studied Although obliteration of the cardiac lymph supply produced fibroelastotic lesions the addition of a plantain diet did not usually produce much increase in cardiac fibrosis and the changes of EMF or CUO were not seen The reasons for this are discussed

My thanks are due to Dr H Naylor for performing the surgical operations on these animals to Dr Kate Packer for anesthetizing them, to Sisters Anne Adams and Sarah Picton as theater sisters, to Miss Seymour Royal Free Hospital for carrying out repeated ECGs on these animals and to the British Heart Foundation for providing a Vickers Patholux microscope with which the pathologic material could be examined and photographed My thanks are also due to Dr M. A. Crawford for his advice and suggestions during the writing of this paper

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Atrial T (Ta) loop in patients with A-V block A trial to differentiate normal and abnormal groups

Hiroshi Hayashi, M D *
Mitsuharu Okajima, M D **
Kazuo Yamada, M D ***
Nagoya Japan

It is well known that the T wave or the T loop, as well as the ST segment, is important in the diagnosis of myocardial ischemia and various other abnormalities of the ventricular myocardium This paper describes a study in which a search is made for comparable diagnostic information concerning pathology of the atrium, by examination of the atrial T (Ta) loop in people with atrioventricular (A V) block The results add to previously reported preliminary results[1] and are compared to findings in separately reported experiments in dogs [2]

Methods

High speed and magnified scalar electrocardiograms (ECG) of the P and the Ta waves were recorded on 16 patients with A V block by the Frank lead system The P and the Ta loops were drawn by hand by plotting the successive instantaneous amplitudes of the P and the Ta waves in the scalar ECG at intervals of 0 01 second The patients were divided into two groups as indicated in Table I

Group A consisted of 12 individuals who had A V block but were almost free of symptoms and had no history of severe cardiac disorders

Group B consisted of four patients with A V block and complications of severe cardiovascular diseases such as myocardial infarction or frequent attacks of angina pectoris

A biophysical ME amplifier BE A11 and an EM062, six channel oscillographic recorder were used for amplification and recording A high cut filter of 100 Hz was used The scalar ECG's were taken at a sensitivity of 3 cm per 100 μV and at a paper speed of 10 cm per second Left inferior and anterior directions of X, Y, and Z axes were regarded as positive The method to measure the angle for the maximum P and Ta vectors and P Ta angles is described elsewhere [2] The components of the atrial gradient in each scalar lead are ÅGx, ÅGy and ÅGz The spatial atrial gradient SÅG, was obtained from these components i e

$$SAG = \sqrt{(\mathring{A}Gx)^2 + (AGy)^2 + (AGz)^2}$$

The method to obtain each component of atrial gradient is described elsewhere [2]

Polar vectors were used in the manner described by Burger and Vaane [3]

Results

Group A Records from one patient in Group A a 63 year old woman who did not have cardiovascular complications except A V block, are shown in Fig 1 The maximum Ta vector was oriented to the right superiorly and anteriorly It was exactly opposite to the direction of the maximum P vector The P and the Ta loops were inscribed in a counterclockwise direction In 12 cases of Group A the mean direction of the maximum Ta vector was −122° 171°, and −91° in the frontal horizontal and left sagittal planes respectively

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Reprint requests Hiroshi Hayashi M D Division of Cardiology Department of Medicine Emory University 69 Butler St S E Atlanta Ga 30303

Research Associate Cardiovascular Research and Training Institute College of Medicine University of Utah Salt Lake City Utah.

Professor of Medicine College of Medicine Fujita Gakuen University Toyoake Japan

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Table I The patients examined in this study

Case No		*Age (yr.)*	*Sex*	*Degree of A V block*	*Clinical symptoms and findings*
Group A					
4	Z. K	73	M	III	None
12	K. I	74	M	III	Hypertension (170/80) palpitation
14	Y O	59	M	III	Hypertension (165/85) palpitation shortness of breath
16	T G	49	M	III	None
17	K M	49	F	III	Shortness of breath
19	M H.	63	F	III	Shortness of breath
21	U H	16	M	II	None
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23	K. Y	64	F	II	Hypertension (176/98) LVH shortness of breath
24	S Y	40	M	I	Shortness of breath on exercise PQ = 0.38 sec
27	Z. M.	[illegible]	M	II	Minor angina pectoris 2 yr ago
28	C O	42	M	III	None
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18	T K.	69	F	III	Complete RBBB arteriosclerosis
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Table II The direction of inscription of the P and the Ta loops and the direction of polar vectors in Group A*

	P loop				*Ta loop*			
		Inscription direction				*Inscription direction*		
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4	PSL	C	CC	CC	ASL	CC	CC	CC
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14	ASL	CC	CC	CC	ASR	CC	CC	C
16	ASL	CC	CC	CC	ASL	CC	CC	CC
17	PSL	8	CC	CC	ASL	CC	CC	CC
19	ASL	CC	CC	CC	ASL	CC	CC	CC
21	ASR	CC	CC	C	AIR	CC	8	C
22	PSL	C	CC	CC	PSL	8	CC	CC
23	PSL	C	CC	CC	PSL	8	CC	CC
24	AIR	CC	C	C	AIR	CC	C	C
27	ASL	CC	CC	CC	ASL	CC	CC	CC
28	PSL	C	8	CC	PSL	C	CC	8

* Frontal plane H, horizontal plane LS left sagittal plane C clockwise rotation CC counterclockwise rotation 8 figure of eight A, anterior P posterior S superior I, inferior R right L, left

(Fig 2 Table III) Its mean magnitude was 39 26 and 35 μV in each of the three planes The direction of the maximum P vector was to the left and inferior in most cases The anteroposterior direction was variable Its magnitude ranged from 36 to 190 μV

The average ratio of the magnitude of the maximum Ta vector to that of the maximum P vector (Ta/P) was 0 34 0 41 and 0 32 in each of the three planes The mean P Ta angle was 190° 195° and 187° in each of the three planes

The Ta loop was inscribed counterclockwise in each of the three planes in seven of the 12 cases (Table II) This included two cases with a figure

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19	ASL	CC	CC	CC	ASL	CC	CC	CC
21	ASR	CC	CC	C	AIR	CC	8	C
22	PSL	C	CC	CC	PSL	8	CC	CC
23	PSL	C	CC	CC	PSL	8	CC	CC
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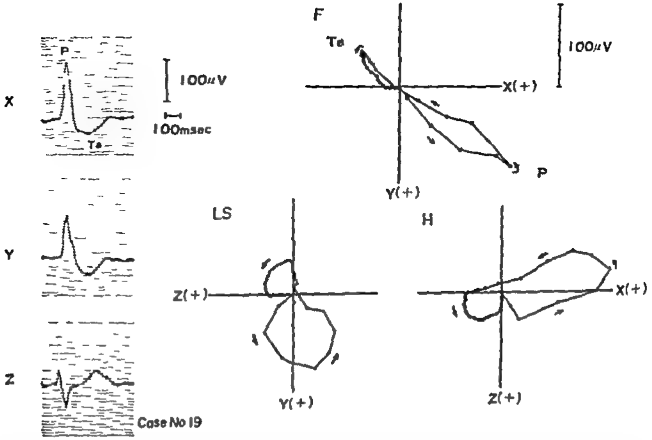

Fig 1 The Ta loop of a patient (M H) in Group A The P and the Ta waves in Leads X Y and Z of the scalar ECG are shown on the left and the graphically composed P and Ta loops are shown on the right F Frontal plane H horizontal plane LS left sagittal plane The P and the Ta waves have opposite polarity in each scalar lead The maximum P and Ta vectors are oriented exactly opposite in each of the three planes The Ta loop is the smaller one with densely dotted portions in each of the three planes of the vectorcardiogram The Ta loop is a long ellipse in the frontal plane and round or circular in the horizontal and left sagittal planes The size or the area of the Ta loop is approximately proportionate to that of the P loop The direction of inscription of the P and Ta loops is the same—counterclockwise in each plane The dots indicate 10 msec intervals for both the P and the Ta loops This applies to Fig 1 through 5

of 8 inscription in one plane but with main direction of inscription counterclockwise The polar vector of the Ta loop was oriented anteriorly superiorly and to the left in five cases The direction of inscription of the P loop was counterclockwise in each of the three planes in four of 12 cases In eight cases of 12 the direction of the polar vector of the P and the Ta loops was the same

Table III summarizes the data of the 12 patients in Group A These results were compared to those obtained from a group of normal dogs studied by similar methodology in our laboratory,[7] and the significance of this comparison is elaborated further in the discussion In all 12 of the normal human patients the spatial atrial gradient was oriented to the left, inferiorly and anteriorly It was small in magnitude with a mean value of 3 5 μVsec and a range from 1 5 to 5 8 μVsec

Group B Records from one patient in Group B a 67 year old man who suffered from inferior myocardial infarction several years ago are shown in Fig 3

The Ta loop was irregular in shape and relatively large compared to the P loop in each of the three planes The direction of the maximum Ta vector was to the left, inferior and anterior The P Ta angle was very narrow in all planes In four cases of Group B the directions of the maximum Ta vectors were 162°, −75° 128° and 72° with magnitudes of 40 20 25 and 38 μV in the frontal plane (Fig 4) These are the values of cases 3, 18 25 and 29 respectively The same order is used in the following

The direction of the maximum P vector in the frontal plane was leftward and inferior in all four cases being 9° in case 3 and around 58° in the other three cases The magnitudes of the maximum P vectors were 142 110 89, and 66 μV The Ta/P ratios of the maximum vectors were 0 28 0 18 0 28 and 0 58 respectively

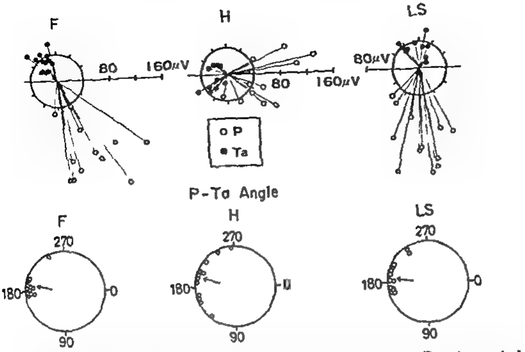

Fig 2 The distribution of the directions and magnitudes of maximum P and Ta vectors and P Ta angles in each of the three planes for Group A patients The maximum Ta vectors are oriented to the right and superiorly The maximum P vectors are directed to the left and inferiorly The P Ta angle was close to 180 degrees in each plane

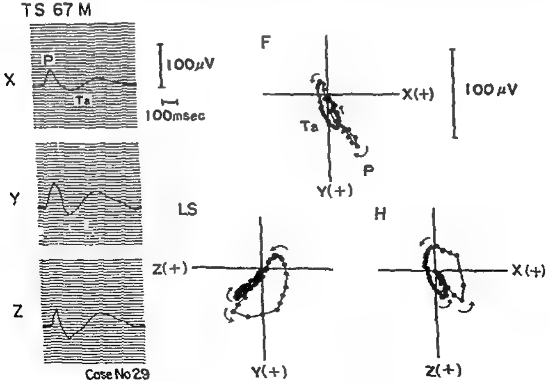

Fig 3 The Ta loop of a patient in Group B The Ta wave is of the same polarity as the P wave in each scalar lead and is relatively large compared to the P wave The Ta loop is irregular in shape and relatively large compared to the P loop The directions of the maximum P and Ta vectors are both to the left inferior and anterior The P Ta angle is very narrow The Ta loop extends to two or three quadrants in all planes

Table III The comparison of the measurements of the P and the Ta loops between 12 patients in Group A and 28 dogs without atrial injury

	Human (Group A)			*Normal dogs*		
	Mean	*Max*	*Min*	*Mean*	*Max*	*Min*
Maximum Ta vector						
Direction (°)						
F	−122	−150	−102	−118	−140	−104
H	171	−160	101	129	161	111
LS	−91	−127	−38	−112	−144	−100
Magnitude (μV)						
F	39	58	20	50	64	32
H	26	52	12	34	43	24
LS	35	57	13	51	65	27
Maximum P vector						
Direction (°)						
F	69	97	36	69	85	40
H	21	100	−29	−32	−57	−6
LS	96	136	64	71	99	61
Magnitude (μV)						
F	120	190	50	278	385	215
H	67	135	36	131	232	50
LS	114	159	58	273	367	202
P Ta angle (°)						
F	190	246	171	183	202	170
H	195	263	130	188	228	170
LS	187	239	156	187	201	174
Ta/P ratio						
F	0 34	0 46	0 18	0 20	0 25	0 15
H	0 41	0 52	0 23	0 28	0 50	0 17
LS	0 32	0 46	0 21	0 19	0 27	0 14
Magnitude of spatial atrial gradient (μvsec)	3 5	5 8	1 5	3 1	5 1	1 4
Direction of inscription of P and Ta loops						
F	CC†	(8/12 cases)		C†	(25/28 cases)	
H	CC	(10/12 cases)		C	(27/28 cases)	
LS	CC	(9/12 cases)		C	(27/28 cases)	

Ta/P ratio magnitude of maximum Ta vector/magnitude of maximum P vector
†Main direction of inscription was determined when the loop is a figure of eight

In the horizontal plane the directions of the maximum Ta vectors were −156°, 102°, 148° and 68°, and magnitudes were 42, 15 12 and 31 μV The directions of the maximum P vectors were leftward and anterior ranging from 18° to 51° Their magnitudes were 150, 75, 54, and 46 μV The Ta/P ratios of the maximum vectors were 0 28 0 20, 0 22, and 0 67

In the left sagittal plane the directions of the maximum Ta vectors were 20°, −125°, 124°, and 127°, and magnitudes were 20, 25, 24 and 47 μV The directions of the maximum P vectors were anterior and inferior, being 159°, 116°, 102° and 123° with magnitudes of 95, 100 74, and 59 μV respectively The Ta/P ratios of the maximum vectors were 0 21, 0 25, 0 32 and 0 80

The P Ta angles were 153°, 132°, 73° and 12° in the frontal plane, 177°, 53°, 130° and 20° in the horizontal plane, and 133°, 108° 22° and 4° in the left sagittal plane The direction of inscription of the Ta loop did not agree with that of the P loop in three cases in the frontal and in two cases in the left sagittal plane (Table IV) The polar vector of the Ta loop was oriented anteriorly superiorly, and to the right in three cases The spatial atrial gradient was oriented leftward infer

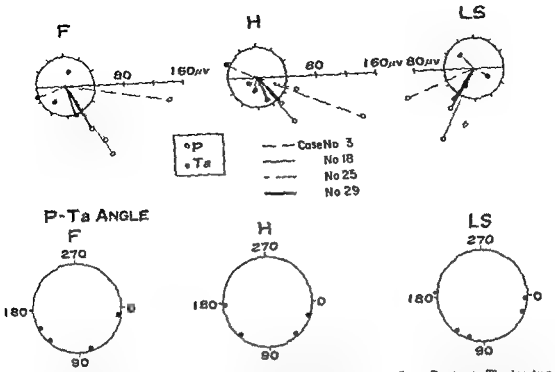

Fig 4 The distribution of the maximum P and Ta vectors and the P Ta angles in Group B patients The direction of the maximum P vectors is to the left inferior and anterior in all cases However the maximum Ta vectors are oriented in different directions The P Ta angle is smaller than 180 degrees in most cases in either plane The Ta/P ratio of the maximum vectors varied a great deal.

Table IV The direction of inscription of the P and the Ta loops and the direction of polar vectors in Group B

	P loop				*Ta loop*			
		Inscription direction				*Inscription direction*		
Case No	*Polar vector*	*F*	*H*	*LS*	*Polar vector*	*F*	*H*	*LS*
3	ASR	CC	CC	C	ASR	8	CC	C
18	ASL	8	CC	CC	PSL	8	CC	CC
25	PSL	C	CC	CC	ASR	CC	CC	C
29	PSL	C	CC	CC	ASR	CC	CC	C

iorly and posteriorly in case 3 leftward inferiorly and anteriorly in cases 18 and 29 and rightward inferiorly and anteriorly in case 25 (Fig 5)

The magnitude of the vector was 1 9 µVsec in case 3 6 7 µVsec in case 18 12 1 µVsec in case 29 and 6 3 µVsec in case 25

Discussion

With improvements in vectorcardiographic recording techniques understanding of the electrical phenomena of the heart has progressed greatly The P loop has been investigated in depth with the use of in particular an electrical dissection method [8] or a magnified recording technique [7,10] However only a few studies have been done on the Ta loop, which represents the repolarization process of the atria This is because the Ta loop is difficult to observe as (1) it is very small in size and (2) under physiologic conditions only the initial portion of the loop is seen since it merges with the QRS loop for the most part

A part of the Ta loop has been observed previously in a transitional portion between the P and the QRS loops when the P loop was magnified a great deal.[8,11,3] Brody and associates [3] recorded the initial part of the Ta loop

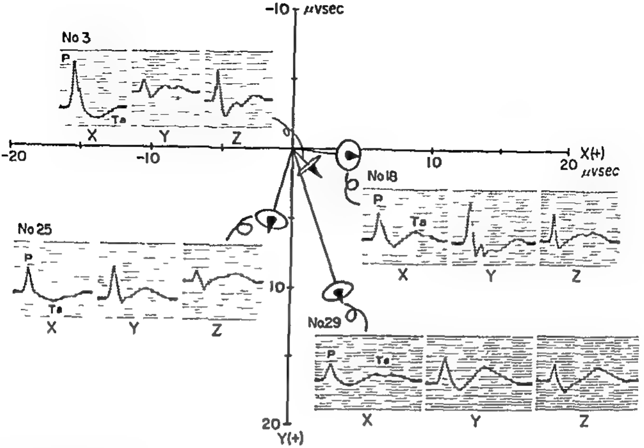

Fig 5 The spatial atrial gradient in Group B patients They are oriented to the left inferiorly and anteriorly in two cases One is to the left inferior and posterior and the other is to the right inferior and anterior Its magnitude is large except in case 3

with the aid of computer averaging We reported previously the normal Ta loop and the Ta loop after atrial injury in dog experiments[1,2] with the magnification of the loop 30 times as large as the usual recording In this paper we compare the Ta loops in human patients with those of dogs with or without atrial injury

Ta loop in Group A The direction of the maximum Ta vector was to the right and superior and the maximum P vector was oriented leftward and inferiorly however anteroposterior direction of both vectors varied In dogs without atrial injury, the maximum Ta vector was oriented rightward, superiorly and anteriorly Both in Group A human subjects and in dogs the P Ta angle was close to 180° in each of the three planes From this fact it is suggested that atrial excitation spreads leftward and inferiorly originating from the sinus node and that the order of atrial repolarization follows that of depolarization both in dog and human atria The magnitude of the maximum Ta vector was nearly proportionate to that of the maximum P vector The relative magnitude of the Ta loop to the P loop in human cases was larger than that in dogs as would be known from the Ta/P ratio (Table III) The Ta loop was mostly a smooth and long ellipse or a circular shape as in dogs without atrial injury The P loop made a transition to the Ta loop without being closed in each of the three planes This may be explained by the lack of the plateau phase in action potential of the atrial muscle

In many of this group and in all normal dogs the P and the Ta loops had the same direction of inscription and P Ta angle was close to 180° in each of the three planes In both this group and normal dogs the direction of the spatial atrial gradient was the same and their magnitudes were very small All these findings provide evidence that atrial recovery process follows almost exactly the excitation process

Ta loop in Group B The Ta loop was irregular in shape The area of the loop was abnormally large or small compared to that of the P loop and the Ta/P ratio of the maximum vectors was also markedly large or small The P Ta angle deviated markedly from 180° These findings were similar to those in dogs with atrial injury[2] and they appeared to be important and clear findings suggestive of atrial abnormalities

In the dog experiments with localized atrial injury, the orientation of the Ta loop correlated

with the site of atrial injury The abnormal Ta loop in Group B patients could likewise be due to localized injury with the orientation of the maximum Ta vector indicating the location of the injury There are no autopsy data to document that possibility and the abnormal Ta loops in Group B could be compatible with diffuse as well as localized atrial disease

The differences of the P loops were minimal compared to those of the Ta loops between Group A and B patients as was also true between those dogs with or without atrial injury This could be due to the fact that in these cases large areas of atrial infarction had not occurred and that atrial disease was not severe enough to alter activation sequence In Group B patients the direction of the spatial atrial gradient varied In three of the four cases the magnitudes of the spatial atrial gradient were markedly large compared to those of Group A

When injury was experimentally made on dog atria the magnitude of the spatial atrial gradient increased markedly and its direction changed systematically according to the site of injury That is it was oriented rightward inferiorly and posteriorly after injury of the right posterior atrial wall and rightward superiorly and anteriorly after injury of the right anterior atrial wall It was oriented leftward inferiorly and posteriorly after injury of the left posterior wall and to the left superiorly and anteriorly after injury of the left anterior wall. It may be unjustified to directly apply the results of dog experiments to human subjects as there are some differences between the two anatomy of the heart the shape of the chest cage the lead system and so on However if the results in dog experiments can safely be applied to human cases the direction of the spatial atrial gradient vector should be useful in identifying the location of atrial lesions That is it is suggested that the atrial injury may exist in the left posterior wall in case 3 in the left posterior or anterior wall in cases 18 and 29 and in the right posterior or anterior wall in case 25 The same reservations stated about the significance of the direction of the maximum Ta vector should be stated here—the abnormal spatial atrial gradient could be due to diffuse as well as localized atrial disease

The direction of inscription of the Ta loop was in the same direction as that of the P loop less often in Group B patients than in Group A This may be a useful diagnostic difference between normals and abnormal subjects but the differences between the two groups were not as clear as for other parameters

Since it was difficult to find sufficiently large samples with A V block for statistical evaluations especially for Group B patients we may have to wait for additional information to confirm the present findings

Summary

The P and the Ta waves were recorded with high fidelity and high amplification The P and the Ta loops were constructed from these waves Human subjects with A V block were used so that the Ta waves could be completely visualized Subjects were separated into two groups one group with minimal clinical evidence of heart disease and another with more severe disease There were great and important differences in the Ta loops between the two groups with minimal differences in the P loops In the patients with minimal heart disease the Ta loop was always oriented to the right and superiorly The P Ta angle was approximately 180° and all patients in this group showed a small spatial atrial gradient oriented to the left and inferiorly These findings are similar to those found in normal dogs reported separately in this JOURNAL. In the group of four patients with more severe heart disease the P Ta angle varied widely and deviated greatly from 180 The spatial atrial gradient was very large in three cases These findings and others such as the direction of the maximum Ta vectors were diagnostically useful in separating the Ta loops of the two patient groups

Results indicate that the Ta loop may be very useful in separating normal from diseased atria in individuals with A V block There are some frequency differences between the Ta wave and the QRS complex If the Ta wave could be extracted from the QRS complex by the use of some kind of filter when A V block does not exist most of the Ta wave could be visualized This along with high fidelity recording techniques may help detect atrial abnormalities in patients without A V block Future development of this equipment as a clinical tool is hoped for

The authors wish to express their appreciation to Dr K Millar for her constructive comments, criticisms, and valuable help in English.

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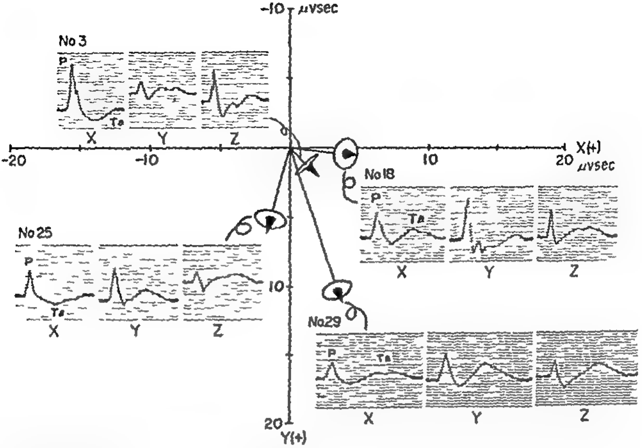

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Case reports

Coronary artery spasm as the cause of myocardial infarction during coronary arteriography

H Jurgen Engel M D
Harry L Page Jr M D
W Barton Campbell M D
Nashville Tenn

Mechanisms of angina pectoris and myocardial infarction in the absence of angiographically demonstrable coronary artery disease have been the subject of numerous recent publications Metabolic changes abnormal enzyme activities abnormal hemoglobin oxygen dissociation curves[2] impairment of oxygen diffusion altered myocardial cell properties disease of small vessels the mitral valve prolapse syndrome[6] and misinterpretation of the arteriogram[8] have all been suggested as possible causes of this enigma Coronary artery spasm has been the central theme of many discussions either occurring spontaneously (as suggested in Prinzmetal's variant angina) or being catheter induced Although coronary artery spasm has been shown to result in transient myocardial ischemia and various potentially lethal arrhythmias myocardial necrosis due to arterial spasm in a nonobstructed coronary artery to our knowledge has been demonstrated only once before An understanding of this possibility and the conditions of its occurrence can be valuable in the analysis of coronary arteriograms as will be shown in the instance we report

Case history

A 43 year-old white woman was admitted to St Thomas Hospital in May 19[illegible] because of severe substernal chest pain with variable radiation into the left jaw left shoulder left arm the upper posterior chest or the right arm These symptoms had begun three months prior to admission and were not always related to exertion The pain was associated with weakness nausea and at times sweating and shortness of breath. The distress was temporarily relieved by nitroglycerin but after about 10 minutes the anginal symptoms would frequently recur and last as long as 30 minutes The patient observed that during these episodes her hands would "turn blue" and her feet would become quite cold The electrocardiogram at that time showed intermittent nonspecific T wave changes (Fig 1) After a cholecystectomy in April 19 0 marked T wave inversion in the precordial leads was observed following severe substernal pain Serial electrocardiograms serum enzymes, and white cell counts failed to show evidence of a myocardial infarction Cervical spine series showed no significant abnormalities A hiatal hernia and other abnormalities of the esophagus and stomach were excluded. On chest x ray the heart was of normal configuration. Serum cholesterol was repeatedly elevated in the range of 270 to 365 mg per cent and triglycerides were elevated to 2.8 mg per cent Glucose metabolism was found to be normal. The blood pressure had never been elevated and the patient denied smoking cigarettes. Physical examination was normal.

Because of persistence of angina like symptoms in spite of medication with isosorbide dinitrate intermittent meperidine and nitroglycerin, selective coronary arteriography was carried out using the Judkins technique Prior to intubation of the right coronary artery 0 4 mg of nitroglycerin was administered sublingually and following each injection of contrast into the right coronary artery the catheter was withdrawn from the ostium. On each injection the proximal right coronary artery was noted to have a long symmetrical, segmental occlusion thought to represent more than 90 per cent loss of the internal cross-section area of the artery (Fig. 2) No collateral vessels were seen into the distal right coronary artery The entire left coronary system appeared to be without disease Following the third injection of the right coronary artery the ST segments in Leads II III and aV_F became markedly elevated with T wave inversions in these leads and the patient complained of severe chest pain Serial electrocardiograms over the next days (Fig 3) continued to show evidence of an injury pattern and permanent Q waves developed in Leads II III and aV_F. The serum glutamic oxaloacetic transaminase (SGOT) rose from 57 to 78 to 147 and the creatine phosphokinase (CPK) from 4 to 70 to 90 over three successive days. The patient had episodes of nodal

From the St Thomas Hospital Department of Cardiology Nashville

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Reprint requests to Dr H J Engel Department of Cardiology St. Thomas Hospital Nashville Tenn 37203

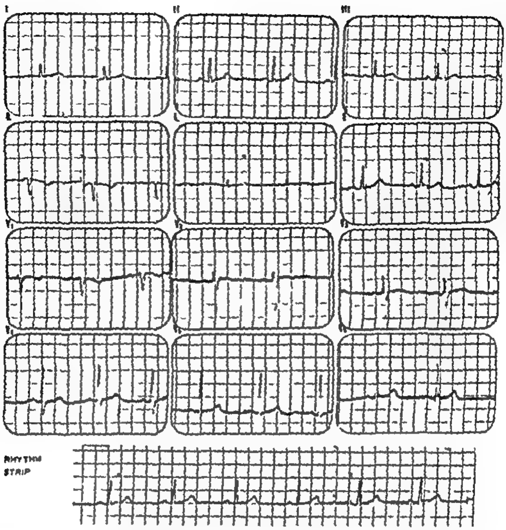

Fig 1 Electrocardiogram on May 15 1970 before the first coronary cineangiography demonstrating mild nonspecific T wave changes

tachycardia and continued to have intermittent chest pain Therefore five weeks after the coronary cineangiography a venous bypass graft from the aorta to the right coronary artery was performed At the time of surgery the proximal and distal right coronary artery were noted to be very soft and pliable The lumen appeared to be uncompromised and there was no evidence of atheromatous disease Her postoperative course was free of complications but she continued to have intermittent chest pain Seven weeks after surgery the ST segments in the precordial leads were again noted to be markedly inverted and repeat coronary cineangiography was performed in August 1970

The repeat study revealed a normal left ventriculogram and a patent venous graft to the distal right coronary artery The proximal right coronary artery was noted to be without evidence of occlusive disease or luminal irregularity The left coronary arterial system continued to be free of visible atherosclerotic changes Various medications failed to relieve the patient s chest pain Because of recurrent severe and at times incapacitating pain a third angiographic study was performed three years later in August 1973 At this time the venous graft was found to be obstructed Again the proximal right coronary artery was free of stenotic lesions or atheros clerotic changes (Fig 4) At the region of the graft anastomosis the lumen of the right coronary artery appeared to be somewhat irregular and narrowed

Discussion

The incidence of myocardial infarction as a complication of coronary arteriography varies from 0 1 to 2 5 per cent in the literature[8] Coronary occlusions during cardiac catheteriza tion usually result from embolization of foreign material from the tip of the catheter or dislodg ment of atheromatous material[10] Subintimal dissection of a coronary artery and prolonged catheter obstruction of a stenotic vessel are other reasons for critical decrease of coronary blood flow that may be particularly inherent to the percutaneous transfemoral approach[11] Meticu lous observation of certain procedural precau tions published by one of the authors[1] has been successful in completely avoiding embolic acci dents in 1 130 coronary arteriograms that were carried out in our cardiovascular laboratory during the past 12 months

The angiographic demonstration of a long seg mental subtotal occlusion of the right coronary artery that was documented during the first

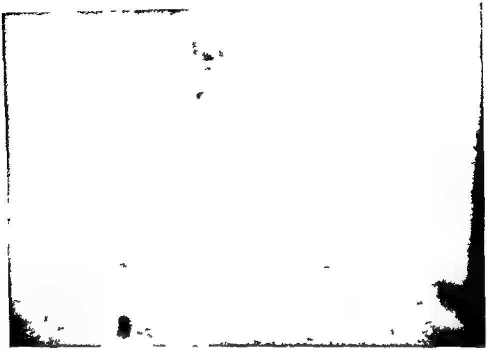

Fig 2 First coronary arteriography on May 20 1970 demonstrating a long segmental proximal stenosis of the right coronary artery in the right anterior oblique projection

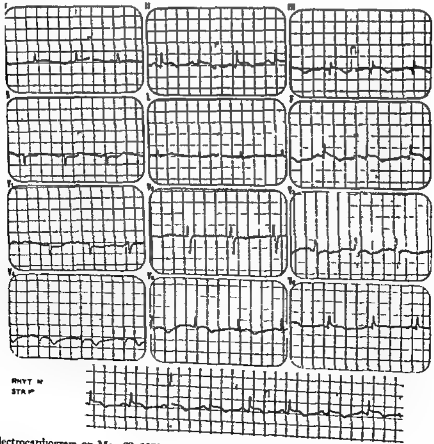

Fig 3 Electrocardiogram on May 22 1970 two days after the first coronary arteriography demonstrating an evolving inferior lateral myocardial infarction

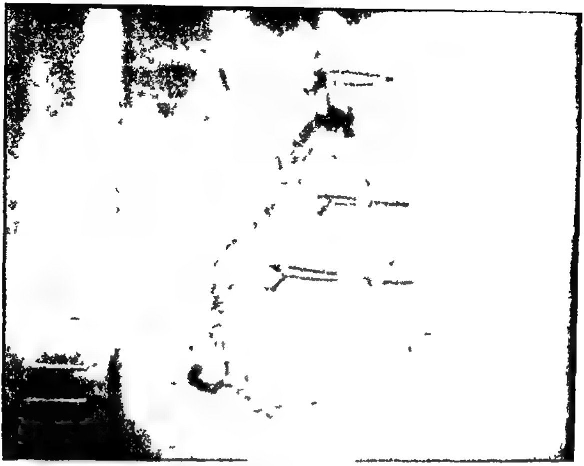

Fig 4 Third coronary arteriography on Aug 22 1973 demonstrating a normal proximal right coronary artery and luminal irregularity and narrowing at the level of the graft anastomosis

procedure (Fig 2) precludes an embolic etiology in this instance Subintimal dissection of coronary arteries is recognized by a peculiar linear stain close to the orifice of the respective artery This was not present in our case We are therefore, led to conclude that severe coronary artery spasm occurred resulting in myocardial necrosis in the inferior left ventricular wall

There is evidence to suggest that segmental arterial contractions are independent from the physiologic regulation of arteriolar coronary blood flow in which local hypoxia vasoactive metabolites such as adenosine and catecholamines play an important role[15,16] The tone of vascular smooth muscle is known to be a function of the intracellular Ca ion concentration which triggers the action of actomyosin ATPase[17] Epinephrine and norepinephrine influence the calcium ion concentration within the smooth muscle cell[18] but the effect of catecholamines on coronary circulation is still somewhat controversial in the literature[18,19] and their role in the production of coronary spasm is unknown

While the exact mechanism of arterial spasm has not been established on the molecular level angiographic experiences offer some clues concerning the circumstances contributing to its existence The problem of functional arterial stenosis during arteriography of various organs has been well recognized for many years and has been the subject of many publications[20,21] Recently, coronary artery spasm has been repeatedly documented during catheterization[22,23] Considerations about the etiology of arterial spasm during angiography have included sudden stretching of the muscle layer of the artery by catheter or guide wire sudden sharp rise of intra arterial pressure by forceful angiography, and mechanical stimulation of the arterial smooth muscle by the presence of a catheter in the vessel[21,24] This explanation is analogous to the hypothesis that mechanical stimulation of the vessel wall is responsible for sustained arterial contraction in perforating gunshot wounds of medium sized arteries[1] In order to recognize local contractions in the region of selective intubation a scout injection into the parent vessel is generally performed in angiographies other than coronary arteriography, and aortic root injections have been recommended in cases of suspected coronary artery spasm[23]

Reports have documented arterial spasm without intubation of the vessel These cases may be due to chemical irritation by the contrast material or to increased sensitivity to catecholamines[2] Spontaneous coronary artery spasm has been seen in cases of Prinzmetal s variant angina[2]

Local contractions usually occur adjacent to the inserted catheter but also have been observed more distally[21] Since in elderly patients the function of arterial smooth muscle tissue is commonly impaired by fibrosis coronary artery spasm is encountered predominantly in younger patients The right coronary artery appears to be more prone to local contractions both secondary to mechanical stimulation by catheter and spontaneously as seen in Prinzmetal s angina[2, 22]

Demany Tambe and Zimmermann[22] report seven cases of coronary artery spasm representing almost 1 per cent of their coronary arteriograms The arterial contractions were associated with chest pain in only three cases and electrocardiographic changes such as patterns of ischemia or injury and an instance of second degree A V block were all readily reversible by administration of nitroglycerin Demany Tambe and Zimmermann defined arterial spasm as disappearance of the luminal narrowing within two minutes after sublingual administration of nitroglycerin In none of their cases did enzyme rises indicate permanent myocardial damage Our observation of sustained arterial contraction in spite of the administration of nitroglycerin and the occurrence of myocardial necrosis secondary to functional narrowing of a coronary artery necessitates a reconsideration of the nature of coronary artery spasm Experiments in dogs have shown that enzyme rises occur after coronary artery occlusion of about 20 minutes duration and that irreversible tissue injury will have taken place after 40 to 60 minutes[2, 7] These findings may not necessarily correspond to the situation in the human but suggest that coronary blood flow must certainly have been critically diminished for more than 20 minutes to produce a transmural infarction The recommendation of Demany Tambe and Zimmermann[22] to perform an aortic root injection after 20 to 30 minutes in cases of suspected coronary artery spasm is therefore somewhat questionable

Another unusual aspect in the patient is the length of the tightly narrowed segment in the proximal right coronary artery The evaluation of stenotic areas within the proximal 2 cm of the right coronary artery can often be difficult[21] In our case the region of spastic contraction extended distally for an unusually long distance Although the morphology of the tightly stenosed segment appeared to be somewhat smooth and lacked the usual ragged appearance of coronary artery disease the findings were misinterpreted because myocardial necrosis due to catheter induced spasm had never been described and subsequent clinical findings provided additional evidence for the diagnosis of organic occlusive coronary artery disease

Since repeated coronary arteriograms failed to demonstrate atheromatous coronary artery disease in the patient the question arises as to the nature of her persistent chest pain Prinzmetal s variant angina must be considered in this setting This syndrome has been shown to result from spasm of atherosclerotic as well as normal coronary arteries It is not provoked by increased cardiac work and is accompanied by certain electrocardiographic features such as transient ST segment elevations and arrhythmias[2] Although it is tempting to ascribe our patient s chest pain to spontaneous spastic activity of her coronary arteries the diagnosis of Prinzmetal s angina cannot be made without the characteristic electrocardiographic criteria

Observations in this patient confirm coronary artery spasm as a cause of myocardial infarction during coronary arteriography However the etiology of her persistent intractable angina pectoris remains undefined and calls for a broader concept in the understanding of ischemic heart disease a concept that may uncomfortably complicate the task of evaluating coronary arteriograms

Summary

Catheter induced coronary artery spasm has been observed frequently It is usually transient reacts to the administration of nitroglycerin and its distribution is generally confined to an area in proximity to the intubated catheter A 43 year old woman with recurrent chest pain was found to have a rather long segment of tight proximal obstruction of the right coronary artery and experienced a myocardial infarction during coronary catheterization Because of recurrent attacks of severe chest pain coronary artery bypass surgery was performed which failed to result in significant improvement of her symptoms Two repeat

coronary cineangiograms seven weeks and three years after surgery revealed the proximal right coronary artery to be free of stenotic lesions or of luminal irregularities After considering possible mechanisms of myocardial necrosis in the presence of normal coronary arteries it is concluded that myocardial necrosis can result from catheter induced coronary artery spasm in spite of administration of nitroglycerin

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Spectrum of sinus node dysfunction in two siblings

Aaron Nordenberg, M.D.
P. Jacob Varghese, M.D., M.R.C.P.
Elizabeth W. Nugent, M.D.
Harrisburg, Pa., and Baltimore, Md.

The sick sinus syndrome or sluggish sinus node has become a well established clinical entity.[1] It has been associated with various clinical conditions including certain congenital heart lesions.[2] Sinus node dysfunction has also been reported in families with and without concomitant electrocardiographic abnormalities of Q-T prolongation and cardiac arrhythmias. In this paper we report two siblings (ages 14 and 23) without any heart disease who demonstrated the spectrum of sinus node dysfunction.

Case reports

Patient No. 1. A 14½-year-old girl was apparently well during childhood. At the age of seven years a routine examination revealed bradycardia and a systolic murmur which was thought to be functional. Her first syncopal episode occurred at the age of twelve years and nine months immediately after swinging on a rope. Physical examination following that attack was unremarkable except for a heart rate of 40 per minute with occasional irregularity and the previously described murmur. Laboratory tests including an electroencephalogram, right heart catheterization, and right atrial angiocardiogram were normal.

The electrocardiogram showed basically an atrioventricular junctional rhythm at the rate of 50 per minute. In some strips 1:1 retrograde conduction to the atria was observed (Fig. 1, *A*). Occasionally, what appeared to be a nonconducted atrial premature beat (as seen after the fourth QRS complex in Fig. 1, *A*) did not disturb the atrioventricular junctional rhythm. In Fig. 1, *B*, on the other hand, three normally conducted sinus beats were followed by a long pause which was terminated by an atrioventricular junctional escape beat. The escape interval corresponded to a rate of 50, similar to the basic junctional rhythm in Fig. 1, *A*. Brief periods of sinus rhythm with long periods of junctional rhythm and no visible P waves are shown in Fig. 1, *C*. Sudden development of such a long pause suggested either sinus arrest or sinoatrial block. Exercise and administration of atropine did not increase the heart rate significantly and confirmed the diagnosis of sinus node dysfunction.

After discharge from the hospital the patient experienced occasional episodes of headache, dizziness, shortness of breath, and palpitations. The next syncopal episode occurred while she was dancing. During another episode, the school nurse counted a radial pulse of 20 per minute. The patient could "avoid fainting" by lying down. She was given sublingual isoproterenol, 5 mg. three times a day, which briefly increased the heart rate to 76 per minute but she complained of palpitations and a "general bad feeling." She was then readmitted to the hospital. The patient was very apprehensive and confined her activities to the irreducible minimum. The physical examination was unchanged except for frequent irregularities of the bigeminal form. All the investigations including electroencephalogram revealed no abnormality.

The electrocardiograms were similar to those obtained previously except for the presence of frequent premature ventricular contractions. The premature ventricular contractions were fixedly coupled to the previous atrioventricular junctional beat and increased in frequency with exercise and sublingual isoproterenol (Fig. 2).

Because of the increase in frequency of symptoms, it was decided to manage the patient with an electronic pacemaker. A transvenous demand pacemaker was used and continuous pacing could be achieved at a rate of 85 per minute. Following insertion of the demand pacemaker, it was apparent that ventricular ectopic activity existed with the slightest exercise and resulted in QRS complexes which were fixedly coupled to the paced beat. This was not controlled by quinidine, 200 mg. every six hours orally alone or in combination with propranolol, 10 mg. three times a day. Since the idioventricular activity might have been due to the movement of the electrode catheter during exercise, a permanent epicardial pacemaker was inserted (Medtronic Model No. 5842). This also did not control the ventricular ectopic activity with exercise (Fig. 3). However, when the propranolol dosage was increased to 20 mg. every six hours, the patient could do a double Master test without having unpaced ventricular beats. Challenge with 5 mg. of isoproterenol orally did not evoke any unpaced rhythms.

From the Pediatric Departments of the Polyclinic Hospital, Harrisburg, Pa., and The Johns Hopkins Hospital, Baltimore, Md.

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Reprint requests: Dr. P. Jacob Varghese, The Helen B. Taussig Children's Cardiac Center, The Johns Hopkins Hospital, Baltimore, Md. 21205.


A

B

C

Fig. 1. *A*, Lead II. Atrioventricular junctional rhythm with a rate of 50 per minute. There is 1:1 retrograde conduction to the atria. A nonconducted atrial premature systole is present after the fourth and eighth QRS complex. This does not disturb the atrioventricular junctional rhythm. *B*, Lead V R. Three normally conducted beats are followed by a long pause suggesting sinus arrest or SA block. The pause is terminated by an atrioventricular junctional escape beat. The escape interval corresponds to a rate of 50, similar to the basic junctional rhythm. A nonconducted P wave is seen 0.56 seconds after the A-V junctional beat; the resultant pause is terminated by a second escape beat. This beat probably originates in a lower region of the A-V junction (longer escape interval) probably because concealed conduction of the blocked P wave discharged the initial junctional pacemaker. The second and third escape beats (fifth and sixth QRS's) are followed by P waves with the same R-P interval (0.16 second)—probably representing retrograde P waves from a lower junctional pacemaker. If this is true, the fourth QRS is probably also followed by a retrograde P wave which is buried in the T wave and therefore the blocked P wave following the fourth QRS can represent atrial premature systole. This interpretation is supported by the presence of another atrial premature systole after the retrograde conduction of the fifth QRS though the coupling interval in the latter instance is shorter (0.44 second). This atrial premature systole is not conducted to the ventricle permitting the appearance of a third escape beat (sixth QRS complex) with a retrograde P. Subsequently a sinus beat occurs with a normal P-R interval at a cycle length similar to the earlier period of sinus rhythm. However, the following P wave of apparently sinus origin was not conducted, strongly suggesting atrioventricular conduction disturbance. *C*, Lead V R. The nonconducted P wave after the fifth QRS is again suggesting abnormal A-V conduction. All the nonconducted P waves in Figs. 1 *A*, *B* and *C* are preceded with another P wave (sinus or retrograde) with a P-P interval of less than 0.7 second. This may suggest abnormal prolongation of the effective refractory period in certain parts of the A-V transmission system. This explanation is challenged by the successful conduction, though with slightly prolonged P-R interval, of the P wave preceding the eighth QRS complex which follows an apparently retrograde P wave at a P-P interval of only 0.42 second. This interval is quite comparable to the coupling interval of the nonconducted atrial premature systole in the middle of Fig. 1 *B*. The evidence given by Figs. *A*, *B* and *C* strongly suggests atrioventricular conduction block, but other mechanisms including concealed atrioventricular junctional discharge could not be ruled out.

Patient No. 2. The 23 year-old sister of the above patient was noted to have a heart murmur and joint pains at the age of seven. She was diagnosed as having possible rheumatic fever and given penicillin twice a day until age 18. After a prolonged syncopal attack at the age of 19 she was admitted to the hospital. Physical examination revealed a slow irregular heart rate of 50 to 60 per minute and a nonspecific ejection systolic murmur. All the laboratory tests, including a right and left heart catheterization, were normal.

Electrocardiogram at the time of admission (Fig. 4 *A*) showed no P waves in any of the leads and a junctional rhythm at a rate of 50 per minute. This junctional rhythm was interrupted with frequent premature ventricular contractions which had a fixed coupling interval. QRS axis of the junctional beat was superior and indicative of a left anterior hemiblock. Lack of Q waves in Leads V and V was suggestive of abnormal septal activation. Absence of atrial activity was confirmed at right heart catheterization. After a standard double Master test the patient developed short runs of ventricular tachycardia (Fig. 4 *B*) which appeared to have morphologic characteristics of bidirectional tachycardia.

The patient moved to another part of the country and was lost to follow up. Recently she was admitted to a local hospital in that area with left hemiparesis of sudden onset. The etiology of the hemiparesis was diagnosed as cerebral embolus originating from the left atrium as a result of prolonged atrial standstill.

There are two other siblings in the family. Both are healthy but in one the electrocardiogram shows an abnormal superior axis. Response to exercise was normal in both siblings. The

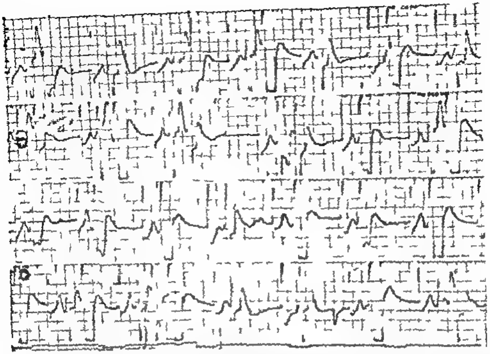


Fig 2 Strip from intensive care unit monitor 30 minutes after administration of 5 mg of isoproterenol sublingually shows multiple premature ventricular complexes of varied configuration The first of each group of *premature complexes has a fixed coupling interval* to the previous nodal complex Note the unusually broad and bizarre QRS complexes that are seen also while the patient is resting without medications

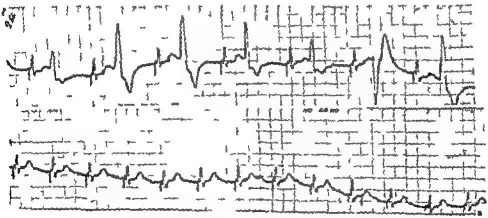
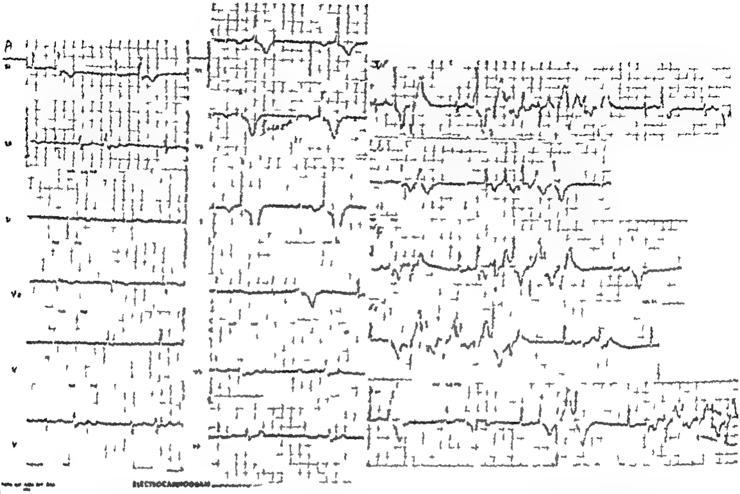


Fig 3 Lead II Electrocardiogram taken immediately after exercise This strip was taken after the insertion of a permanent epicardial demand pacemaker The patient was treated with quinidine 200 mg four times a day and propranolol 10 mg four times a day Note the *persistence of ventricular premature beats*. In the lower panel, the ventricular ectopic focus is overdriven by increasing the rate of the pacemaker

mother of these siblings has no cardiovascular symptoms but the electrocardiogram shows widespread nonspecific T wave changes

Discussion

The two patients presented in this paper illustrate the natural history of the sick sinus syn*drome as well as various complications* of this disease Ferrer[a] reported that sinus bradycardia may be the first presenting feature of the sick sinus syndrome (SSS) *in adults* It appears the presenting feature may be the same in children as shown by both of our patients They presented at the age of seven with a *slow heart rate* The next



A B

Fig 4 A electrocardiogram taken at rest from the patient s 21 year old sister Atrioventricular junctional rhythm with no visible P waves Note the multiple premature ventricular complexes with fixed coupling to the nodal beat Junctional beats have a superior axis on the frontal plane B same patient as in 4 immediately after a double Master s test shows runs of premature ventricular complexes of varied configuration suggestive of bidirectional tachycardia The first ventricular complex in each run is fixedly coupled to the nodal beat

phase in the natural history of the disease is periods of sinus arrest with various escape rhythms Our first patient during a five year period progressed from the first phase of sinus bradycardia to the second phase of brief periods of sinus arrest (Fig 1) The next stage in the disease is for the patients to develop various types of ectopic tachycardias Both of our patients developed such rhythms Ferrer suggested that in this disease the sinus node may die slowly taking five to ten years or more to cease functioning completely Our second patient represents the last stage of this disease presenting at the age of 19 (12 years after the first visit with sinus bradycardia) with atrial standstill and a slow junctional rhythm Thus the whole spectrum of the sick sinus node syndrome is demonstrated in these two siblings

Junctional and ventricular escape rhythms and tachycardia are very common in SSS In both of our patients the escape rhythm was of ventricular origin and increased its frequency on exercise The underlying mechanism of these arrhythmias is not clear One possibility is enhanced rate of an ectopic focus due to sympathetic stimulation It has been shown by various investigators that an increase in sympathetic tone or administration of catecholamines could cause ventricular tachyarrhythmia either by enhancement of the rate of diastolic depolarization in Purkinje fibers or by facilitating re entry through increased temporal dispersion of repolarization in the ventricular muscle The other possibility is that the slow basic rhythm of these patients predisposes them to development of extrasystole and tachycardia It has been demonstrated that

uniform recovery of the ventricle is rate dependent. With a slower rate recovery is less uniform and this facilitates re-entry of an extrasystole and tachycardia.[3]

It is important to know the mechanism of tachycardia because proper management depends on this knowledge. If the underlying mechanism of arrhythmia is due to enhanced activity of an ectopic focus, one may want to use an antiarrhythmic drug to suppress the ectopic focus. This carries a grave danger since the antiarrhythmic drug may also suppress the focus of the slow basic rhythm which could result in asystole of the heart.

On the other hand, the arrhythmia may be the result of a slow basic rhythm. If this were the case, increasing the basic rate by using an electronic pacemaker should control the arrhythmia. A third possibility is that the arrhythmia may be the result of a combination of these factors as in our first patient.

It is possible to suppress an ectopic focus by pacing at a faster rate than the frequency of the focus. This method of overdrive suppression has been used successfully in clinical situations,[1,2] but sometimes one may have to resort to unphysiologic rates to suppress the focus, especially if it is responding to normal catecholamine stimulation as demonstrated by both of our patients. A disadvantage of a fast pacing rate is the prolonged suppression of the normal escape foci. The degree of suppression of an ectopic focus is directly related to the pacing rate.[11] To avoid this problem in such situations, a combination of pacemaker and antiarrhythmic drugs should be used. In our patient No. 1 we were able to pace her at a physiologic rate by adding a combination of antiarrhythmic drugs.

Atrial thrombus and systemic embolization have been recognized as a complication of prolonged atrial standstill.[3] In our patient No. 2 the episode of left hemiparesis must have been the result of a cerebral embolus originating from the left atrium. This problem has not been reported as a complication of SSS; an explanation may be that one does not usually see the end stage of this syndrome. It also raises the interesting question regarding the etiology of the so-called "silent atrium." Is the "silent atrium" an end stage of the SSS?

In summary, we would like to reiterate the words of Dr. Ferrer:[9] "It is urgent, however, to disseminate the concept that not all sinus bradycardia is benign." As we have shown, sinus bradycardia may be the first presenting sign of the SSS and a "silent atrium" may be the end stage of this disease.

Summary

Two siblings, ages 14 and 23, with various features of sinus node dysfunction have been reported. Sinus bradycardia was the presenting feature in both patients. During the follow-up period both patients developed various types of ectopic rhythms which increased with exercise. One of them developed "silent atrium" at the age of 23 and had cerebral embolus as a complication. The other patient had frequent syncopal episodes and had to be treated with a combination of electronic pacemaker and antiarrhythmic drugs.

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Clinical pathologic conference

Savitri Shrivastava M D D M
James H Moller M D
Murthy Tadavarthy M D
Toyoki Fukuda M D
Jesse E Edwards M D
St. Paul and Minneapolis Minn.

DR. SAVITRI SHRIVASTAVA This white female infant was the product of a 32 week uncomplicated pregnancy and delivery She had been tachypneic and a poor feeder since birth and was referred for evaluation at 5 days of age because of increasing tachypnea and diaphoresis On physical examination the patient weighed 3 590 grams and was severely dyspneic pale dusky and mottled gray in appearance The rectal temperature was 94 F and the pulse rate was 190 per minute The pulse was poor in volume the respiratory rate was 150 per minute and the blood pressure was unobtainable There was no edema The first cardiac sound was normal and the second sound was single A prominent third sound was present No murmurs were heard The hepatic edge was palpable 6 to 7 cm below the right costal margin and the splenic tip was palpable

Blood gases were pH of 7 05 P_{CO_2} 17 mm Hg P_{O_2} 32 mm Hg Serum sodium was 131 mEq per liter and potassium was 6 7 mEq per liter The hemoglobin concentration was 16 9 Gm per 100 ml the hematocrit was 74 1 per cent and the total leukocyte count was 16 000 per cubic millimeter The differential leukocyte count was as follows polymorphonuclear leukocytes 51 lymphocytes 40 eosinophils 5 monocytes 4 per cent

The electrocardiogram (ECG) revealed sinus tachycardia and normal P waves The frontal plane QRS axis was +135° The precordial leads showed an Rs pattern in Leads V_4R and V_1 and a QR pattern in Leads V_5 and V_6 There was however no evidence of ventricular hypertrophy

The thoracic roentgenogram showed generalized cardiomegaly and prominence of the pulmonary vasculature (Fig 1) No specific chamber enlargement could be identified nor was the cardiac contour specific for any abnormality

Echocardiograms showed a normal tricuspid valve and paradoxical motion of the ventricular septum suggesting volume overload of the right ventricle In addition recordings of the ventricular septum below the tricuspid valve were suggestive of a ventricular septal defect The pulmonary valve appeared normal The left atrial cavity appeared enlarged but this could have been artificial secondary to transducer position The mitral valvular excursions were diminished and the E F slope delayed The left ventricular cavity appeared to be about three quarters as large as anticipated normal The diameter of the aorta was normal as were the aortic cusps

After 4 hours of treatment with digitalis Lasix Isuprel and sodium bicarbonate the infant s condition improved Blood pressures were then obtainable by the flush method and found to be equal in the upper and lower extremities

Dr Moller will you discuss the differential diagnosis of this case?

DR JAMES H MOLLER This neonate presented the cardinal findings of cardiac failure tachycardia tachypnea hepatomegaly and cardiomegaly Additional features suggesting this state were diaphoresis and the history of poor feeding Cardiac failure occurring at this age usually results from one of four hemodynamic states arteriovenous fistula myocardial disease valvular insufficiency or an obstructive lesion

From the Department of Pathology United Hospitals–Miller Division St Paul, Minn., and the Departments of Pathology Pediatrics and Radiology University of Minnesota, Minneapolis, Minn

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Reprint requests Jesse E Edwards, M D Department of Pathology United Hospitals–Miller Division, 125 W College Ave St Paul Minn. 55102.

Fig 1 Frontal view of thoracic roentgenogram

Arteriovenous fistula is an uncommon cause of neonatal cardiac failure, but when it occurs may be profound and unresponsive to medical management In my experience, neonates with this condition do not present an ashen gray appearance and may have sharp peripheral pulses Usually, the ECG reveals right atrial enlargement and right ventricular hypertrophy in contrast to the pattern described in this patient Absence on the echocardiogram of an enlarged left ventricle is against this diagnosis

Myocardial disease in the form of myocarditis could present this clinical picture but is also uncommon The ECG should show ST and T wave changes and the roentgenogram, a large heart In addition, the echocardiographic evidence of an enlarged left ventricle should be present

Valvular insufficiency of the tricuspid pulmonary, or mitral valve has been reported to cause cardiac failure in the newborn infant Usually the heart is greatly enlarged and the ECG shows more abnormalities Ventricular enlargement accompanies valvular insufficiency and should have been evident in the echocardiogram

Obstructive lesions in the left side of the heart are the most frequent cause of neonatal cardiac failure In order of decreasing frequency, these are (1) aortic valvular atresia with or without coexistent mitral atresia, (2) coarctation of the aorta, (3) severe aortic stenosis with either a normal sized or hypoplastic left ventricle, and (4) obstructive conditions of the mitral valve

Each of these conditions leads to a picture of profound cardiac failure in the newborn period Low cardiac output is a principal feature manifested by mottling of the skin an ashen color, weak or absent peripheral pulses, and low or unobtainable blood pressure

In neonates with coarctation of the aorta because of the low cardiac output and low levels of arterial pressure a difference in pressure between the arms and legs may not be obtained Thus even coarctation cannot be distinguished on physical examination Because of the reduced cardiac output a murmur is often absent in neonates with any of the left sided obstructive lesions

In those conditions with obstruction in the aorta or at the aortic valve, cardiac enlargement is prominent Aortic atresia typically reveals the largest heart the earliest of any cardiac condition Severe aortic stenosis or coarctation of the aorta with cardiac failure show a similar roentgen picture In this patient, however, the thoracic roentgenogram revealed only mild cardiomegaly, which may indicate obstruction at either the mitral valve or at a site more proximal

The ECG may be helpful in distinguishing conditions causing left sided obstruction Aortic atresia can be virtually excluded, I believe because Q waves were present in Leads V_5 and V_6 I have never seen a patient with aortic atresia with this finding Coarctation of the aorta can also be virtually eliminated because of the presence of normal T waves in the precordial leads Most infants with coarctation of the aorta that results in congestive cardiac failure show a pattern of right ventricular hypertrophy and inverted T waves in the left precordium the latter suggesting left ventricular strain additionally, neonates with aortic stenosis and normal sized left ventricles show left ventricular hypertrophy and strain Therefore the ECG tends to exclude aortic atresia coarctation of the aorta, and aortic stenosis with normal sized left ventricle

The echocardiogram is very helpful in identifying that the left ventricle was hypoplastic as this would also eliminate isolated coarctation of the aorta and aortic stenosis with a *normal left* ventricular cavitary size

The echocardiographic finding of a hypoplastic

Fig 2 A B Angiocardiograms. A Left atriogram B Right ventriculogram

left ventricle could indicate aortic atresia with patent mitral valve aortic stenosis with hypoplastic left ventricle or mitral stenosis Frequently in neonates and infants with aortic obstructive lesions the mitral valve is abnormal The echocardiographic finding of the ventricular septal defect would exclude aortic atresia and aortic stenosis because the ventricular septum is intact in these conditions

We are left then with an abnormality of the mitral valve causing stenosis and a coexistent ventricular septal defect Obstructive conditions in the left atrium such as cor triatriatum can be excluded because of the identified abnormality of the mitral valve

Congenital mitral stenosis may be caused by a parachute mitral valve obstruction from large papillary muscles or mitral arcade Only the first of these conditions has been associated with a ventricular septal defect Therefore my diagnosis is mitral stenosis and ventricular septal defect leading to a circulatory pattern similar to mitral atresia Mitral atresia may be excluded since the mitral valve however abnormal was identified in the echocardiogram Classically in mitral atresia there is no mitral valvular tissue

Dr Shrivastava Cardiac catheterization was performed from the right saphenous vein (Table I) Although the catheter tip could be advanced from the right atrium into the left atrium it could not then be advanced into the left ventricle despite repeated attempts The failure of the catheter to enter the left ventricle from the left atrium could mean obstruction of the mitral valve The blood in the left atrium was fully saturated with oxygen and there was an increase in oxygen saturation of blood in the right atrium indicating a left to right shunt at the atrial level.

Fig 2C Aortogram.

Table I Cardiac catheterization data

Site	Pressure (mm Hg)	Oxygen saturation (%)
Inferior vena cava	–	75
Superior vena cava	–	51
Right atrium	A 13 V 16 Mean 11	86
Right ventricle	60/0 13	84
Pulmonary artery	80/40 Mean 60	86
Left atrium	A 13 V 16 Mean 11	99
Left brachial artery	–	88

Oxygen was administered throughout the procedure

In addition the left brachial arterial blood was 88 per cent saturated which, in the presence of fully saturated left atrial blood indicates a right to left shunt at either the ventricular or ductal level

Studies of pressures showed the mean atrial pressures to be identical at 11 mm Hg The fact that they were equal supports the diagnosis of an atrial septal defect although usually in this condition the pressure level is considerably lower If there were however obstruction to left ventricular filling this could elevate the pressures of each atrium in the presence of an atrial septal defect The pulmonary arterial pressure (80/40 mm Hg) was elevated which in the presence of a normal left atrial pressure, indicates precapillary pulmonary hypertension No gradients were present across the pulmonary or tricuspid valves Several angiograms were performed

Dr Tadavarthy would you please present these?

Dr Murthy Tadavarthy Initially, contrast material was injected into the left atrium (Fig 2, *A*) This study revealed no obvious flow of contrast material from the left atrium across the mitral valve to the left ventricle Instead, the contrast material flowed into the right atrium across the atrial septum From the right atrium the right ventricle opacified and subsequently the left ventricle was opacified presumably through a ventricular septal defect The great vessels were normally related

This angiographic sequence is similar to that in mitral atresia in showing a left to right shunt at atrial level and a right to left shunt at ventricular level Usually, however, in mitral atresia the left atrium is smaller than the one present in this patient It is possible that this patient has some other type of obstruction to mitral flow and a coexistent ventricular septal defect

The second angiocardiographic procedure was a selective right ventriculogram (Fig 2, *B*) This showed that following opacification of a large right ventricle the pulmonary trunk and the left ventricle were opacified the latter through a ventricular septal defect, with subsequent opacification of the normally positioned ascending aorta The opacified left ventricle was at least one third to one half the size of the right ventricle Opacification of the descending aorta appeared to be through a 'reversing patent ductus arteriosus

The final angiocardiographic examination was an aortogram performed from the left brachial artery (Fig 2 *C*) Severe tubular hypoplasia of the aorta was observed between the left subclavian artery and the ductus arteriosus associated with poststenotic dilatation of the descending aorta A localized coarctation at the junction with the ductus was not excluded

In summary this patient has severe mitral valvular obstruction, either atresia or stenosis, and associated ventricular septal defect, tubular hypoplasia of the aortic arch, patent ductus arteriosus and normally related great vessels Classical coarctation could not be excluded

Dr Shrivastava Thank you, Dr Tadavarthy

Following the studies described, a balloon atrial septostomy was performed The patient s physical condition deteriorated and death occurred at the age of 5 days

Dr Fukuda, would you please present the pathologic findings?

Dr Toyoki Fukuda The significant findings at autopsy were confined to the heart and great vessels The heart was markedly enlarged and the anterior surface was formed by the right ventricle, the anterior interventricular sulcus being displaced to the left The great vessels were normally related and the diameter of the pulmonary trunk was twice that of the ascending aorta The right atrium was markedly dilated and hypertrophied Signs of a recent atrial septostomy were evident by laceration of the valve of the foramen ovale and, in addition a small atrial

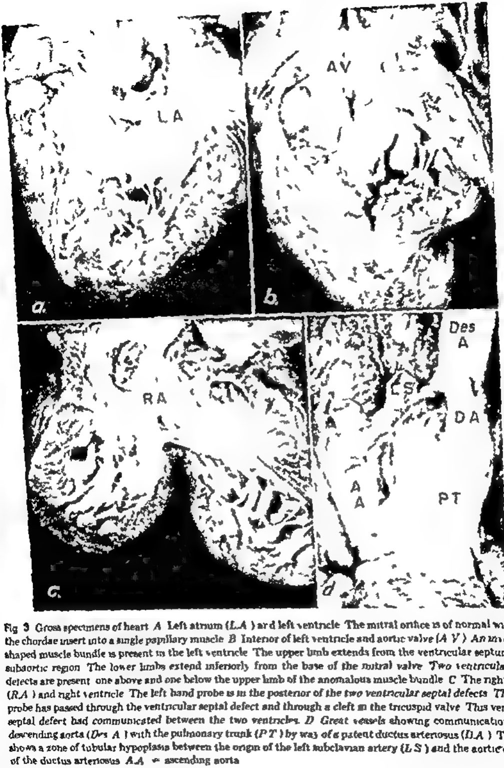

Fig 3 Gross specimens of heart *A* Left atrium (*LA*) and left ventricle The mitral orifice is of normal width and the chordae insert into a single papillary muscle *B* Interior of left ventricle and aortic valve (*A V*) *An inverted V* shaped muscle bundle is present in the left ventricle The upper limb extends from the ventricular septum to the subaortic region The lower limbs extend inferiorly from the base of the mitral valve Two ventricular septal defects are present one above and one below the upper limb of the anomalous muscle bundle C The right atrium (*RA*) and right ventricle The left hand probe is in the posterior of the two ventricular septal defects The upper probe has passed through the ventricular septal defect and through a cleft in the tricuspid valve Thus ventricular septal defect had communicated between the two ventricles *D* Great vessels showing communication of the descending aorta (*Des A*) with the pulmonary trunk (*P T*) by way of a patent ductus arteriosus (*DA*) The aorta shows a zone of tubular hypoplasia between the origin of the left subclavian artery (*L S*) and the aortic entrance of the ductus arteriosus *AA* = ascending aorta

septal defect at the lower edge of the fossa ovalis was evident (Fig 3 *A*)

The left atrium was slightly enlarged and there was a mitral valve with two leaflets The chordae of these converged to insert into a solitary papillary muscle The latter was inserted into the posterior free wall of the left ventricle The mitral valvular deformity was that of a parachute valve but with wide spaces between the chordae tendineae (Fig 3 *B*) The left ventricle showed concen

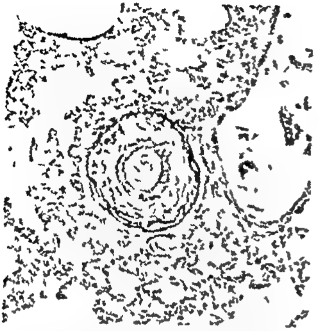

Fig 4 Photomicrograph of muscular artery of the lung Medial hypertrophy associated with considerable thickening of the adventitia (Elastic tissue stain × 91)

tric hypertrophy which resulted in a marked decrease in volume of its cavity the volume of the cavity of the left ventricle being about one third that of the right ventricle An inverted V shaped anomalous muscle bundle was present in the left ventricle (Fig 3, *B*) The apex of the inverted V attached to the base of the left ventricle at a point between the aorta and the base of the anterior mitral leaflet The anterior limb of the anomalous muscle measured 8 mm in width, passed across the left ventricular outflow tract, and attached to the anterior free wall near the septum The posterior limb ran adjacent to the mitral ring, formed the superior rim of the posterior of two ventricular septal defects and attached to the posterior free wall of the left ventricle A second ventricular septal defect lay subjacent to the aortic valve A probe could be passed behind the anterior limb of the muscle bundle from one of the ventricular septal defects to the other

The right ventricle showed dilatation and hypertrophy of its wall measuring 6 mm in thickness (Fig 3 *C*) The two ventricular septal defects were evident One of these (3 by 3 mm) was located at the membranous portion of the ventricular septum and appeared near a cleft between the septal and anterior tricuspid leaflets The other (6 by 4 mm) lay more posteriorly The septal band of the crista supraventricularis was hypertrophied and continuous with an anomalous muscle bundle which was attached to the anterior free wall of the right ventricle The *pulmonary trunk* was dilated and a large patent ductus arteriosus (4 mm in diameter) joined the descending aorta distal to a zone of tubular *hypoplasia of the aortic arch* Tubular hypoplasia of the aortic arch was present between the origin of the left subclavian artery and the junction with the patent ductus arteriosus (Fig 3, *D*) There was no coarctation of the aorta

Histologic examination of the lungs revealed features seen in pulmonary venous obstruction The muscular arteries showed moderate degrees of medial hypertrophy associated with prominently fibrotic adventitial layers (Fig 4) The capillaries were engorged and tortuous (Fig 5 A) The veins showed hypertrophy of their walls and the interlobular septa were edematous and contained dilated lymphatics (Fig 5 *B*)

Dr Shrivastava Thank you Dr Fukuda Dr Edwards, would you please comment on the findings in this case?

Dr. Jesse E Edwards The clinical findings, including results of cardiac catheterization and angiocardiography gave evidence of significant obstruction to the flow of blood into the left ventricle The histologic changes in the lungs were also consistent

The question remains as to whether the obstruction was on the basis of restricted size of the left ventricle or whether there was obstruction at the mitral valve A small left ventricle associated with ventricular septal defects should not affect inflow obstruction into this chamber

The angiocardiographic findings described by Dr Tadavarthy suggest strongly that there was obstruction of the mitral valve Except for the fact that there was slight opacification of the left ventricle following selective injection of contrast material into the left atrium the picture borders on one of mitral atresia

The pathologic examination showed the leaflets and chordae of the mitral valve to be normal while there was only one papillary muscle yielding a parachute mitral valve

A parachute mitral valve may be obstructive on the basis of narrow interchordal spaces As the latter were wide in this case I do not believe that the mitral valvular obstruction is to be ascribed to the parachute valve in this case Rather the anomalous muscle bundles of the left ventricle a

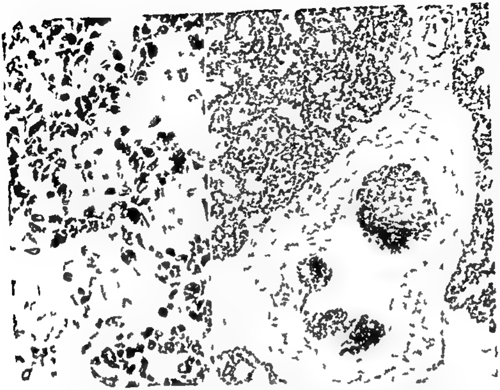

Fig 5 Photomicrographs of lungs *A* Engorgement and tortuosity of capillaries. (Hematoxylin and eosin × 370) *B* Hypertrophy of an intrapulmonary vein and associated edema of interlobular septum (Hematoxylin and eosin × 43)

condition uncommon in this chamber may in some way have compromised opening of the mitral valve

If in fact the left ventricular muscle bundles had prevented adequate opening of the mitral valve I have not seen an exact duplicate of this case On the other hand we have observed mitral valvular obstruction caused by excessively prominent papillary muscles associated with short chordae[1]

It will be recalled that a reversing ductus was demonstrated in the case presented This brings up for consideration the subject of reversing ductus in the young It is possible for a right to left shunt to occur through a ductus in an infant without other anomalies This unusual occurrence may be a reflection of unusual degrees of pulmonary arteriolar vasoconstriction as might occur in hypoxic states The usual instance of reversing ductus in an infant as in the case presented is a reflection of severe obstruction at some point in the circulation downstream from the pulmonary arteries

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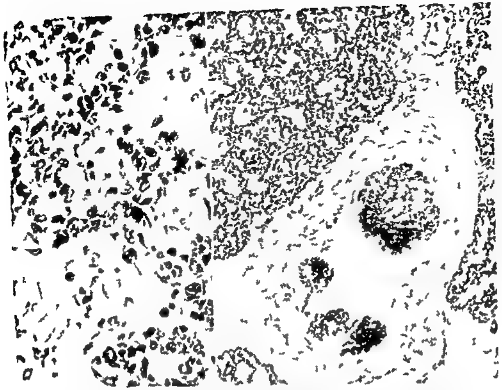

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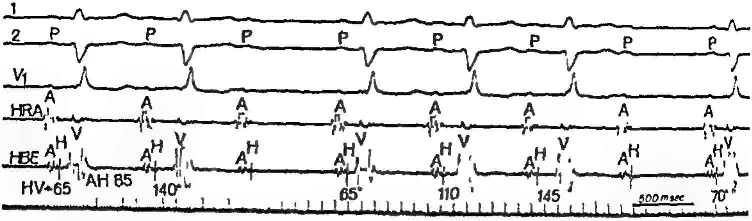

Fig 2 Type I second degree A V block within the HPS in a patient with RBBB and left anterior hemiblock The figure demonstrates a 3 2 and a 4 3 Wenckebach periodicity in which the site of delay and block is below the bundle of His The ECG registers measurable P R prolongations from beat to beat and significant P R shortening following the block beat (a shortening of 75 msec) A V nodal conduction time (i.e., A H interval) is constant at 85 msec and the P R prolongation is accounted for by delay in the HPS

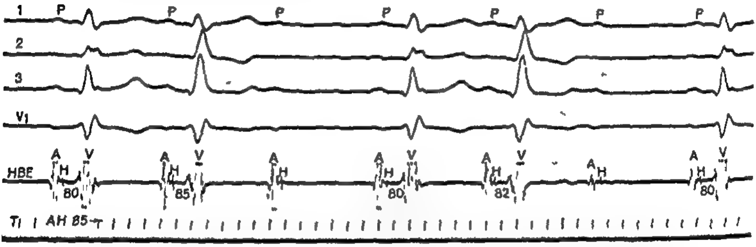

Fig 3 Type I second degree A V block within the HPS The tracing displays two cycles of 3 2 A V conduction The QRS complexes of conducted beats show a fixed RBBB and increasing right axis deviation The third atrial impulse blocks without prior discernible P R prolongation HBE demonstrates constant and normal A H intervals and a subtle H V prolongation prior to block of the third atrial impulse within the HPS

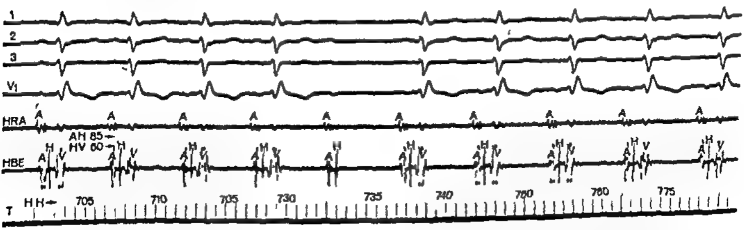

Fig 4 Type II second degree A V block within the HPS During sinus rhythm the A H and H V intervals measure 85 and 60 msec respectively The P R intervals are within normal limits The fifth atrial impulse unexpectedly blocks below the bundle of His without prior H V prolongation In this case the block did not appear to be cycle length dependent since it is preceded by shorter H H intervals and is followed by longer H H intervals with 1 1 A V response

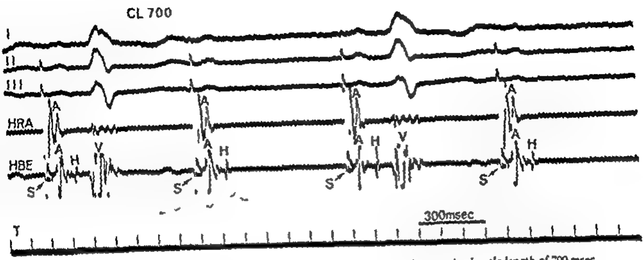

Fig 6 2 1 A V block within th HPS A 2 1 A V block in the HPS is present at an atrial cycle length of 700 msec The P R interval of conducted beats is at the upper limits of normal and the QRS complexes have a LBBB pattern *S represents stimulus artifact*

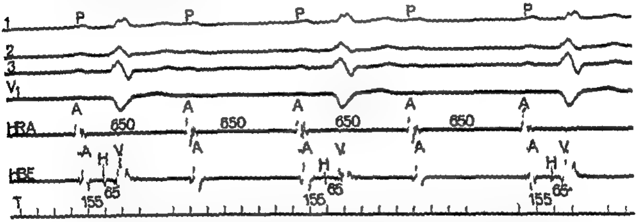

Fig 6 2 1 A V nodal block in a patient with LBBB At sinus rhythm the site of block during 2 1 A V conduction is the A V node The P R interval is slightly prolonged The QRS morphology is very similar to that shown in Fig. 5 The site of block will be difficult to determine without HBE in this and similar situations

dard ECG recordings taken at a paper speed of 25 mm per second mimics classical type II or Mobitz II block (see below)

Type II second degree A V block (Mobitz II) Sudden and unexpected block of a P wave without prolongation of the preceding P R intervals has been termed Mobitz II or type II second degree A V block[1] (Fig 4) In this form of block the QRS morphology usually shows a BBB pattern The P R interval of conducted beats is frequently within normal limits which makes block of the P wave appear unexpected Electrophysiological studies have confirmed that the site of block is always within the HPS Some cases of Mobitz type II block in all probability are examples of subtle Wenckebach type of conduction in the HPS (Fig 3) Conversely a subtle Wenckebach type of conduction within the A V node may mimic a type II second degree A V block A significant shortening of the P R interval following the blocked beat suggests that the A V node is the site of block

High degree (2 1 3 1) A V block In fixed high degree A V block it is difficult by ECG tracings alone to precisely localize the site of block especially when the QRS complexes are abnormal When the QRS complexes are normal the site of block is most often within the A V node but occasionally is within the bundle of His itself High-degree A V block in association with BBB patterns may be within the HPS or the A V node (Figs 5 and 6)

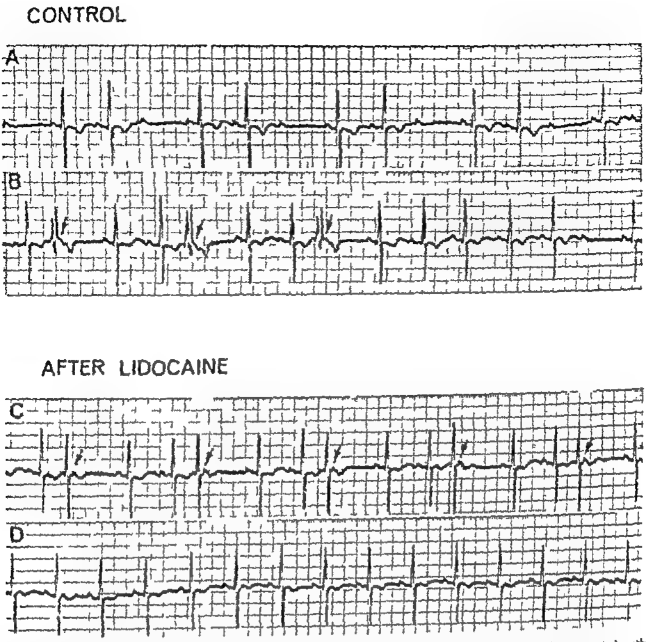

Fig 7 A V block due to concealed bundle of His extrasystoles Panel A shows 3 2 A V block associated with narrow QRS complexes (Lead V1) The P R intervals of conducted beats are normal and no P R prolongation is observed prior to the block Analysis of long rhythm strips (panel B) revealed periodic occurrence of premature QRS complexes with a RBBB pattern just preceding the blocked P waves (arrows) These premature QRS complexes most probably result from aberrant conduction of impulses originating in the region of the bundle of His Retrograde penetration into the A V node induces block of the oncoming (panel B) sinus beats (retrograde concealed conduction in the A V node) When premature His bundle extrasystoles failed to propagate to the ventricles but did propagate retrogradely into the A V node the subsequent P waves were suddenly and unexpectedly blocked (panel A) After an initial lidocaine bolus (1 mg per kilogram) bundle of His extrasystoles conducted to the ventricles with narrow QRS complexes (panel C) and finally were abolished and 1 1 A V conduction was restored (panel D) The normalization of the premature QRS complex which occurred from either shortening of the relative refractoriness of the HPS or slight shortening of the preceding ventricular cycle length (or both) further attest to the origin of premature impulse in the bundle of His

Third degree A V block Third degree A V block refers to complete absence of A V conduction (although V A conduction may be present) ' This site of block can be reasonably predicted from the morphology of the QRS complexes and the rate of the escape pacemaker When the site of block is in the A V node the subsidiary pacemaker is usually located within the bundle of His and the QRS morphology is normal or the same as prior to block In addition ventricular rate is frequently > 40 per minute when the subsidiary pacemaker is located in the bundle of His When the pacemaker is subjunctional (idioventricular) the ventricular rate is usually < 40 per minute

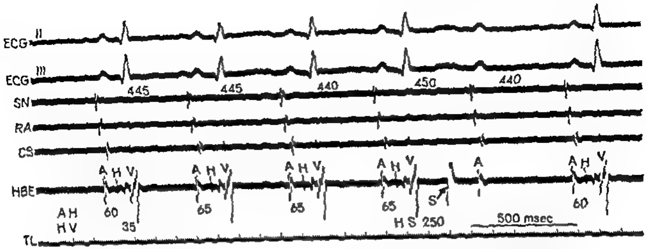

Fig 8 Type II second-degree A V block experimentally induced by programmed bundle of His stimulation Following the fourth sinus beat the bundle of His is electrically stimulated (S) at an H S interval of 250 msec There is no ventricular response because the distal bundle branch Purkinje system is refractory However retrograde concealment in the A V node results in unexpected block of the fifth sinus beat

and the QRS complexes are wide HBE recordings are required to substantiate the uncommon situation of intra His bundle block associated with a junctional pacemaker

In all forms of A V block important clues as to the site of conduction delay or block may be uncovered from ECG recordings taken during exercise or following administration of drugs which affect autonomic balance Delay or block within the A V node usually improves with exercise atropine or isoproterenol administration whereas delay and block within the HPS do not However failure to improve conduction with these maneuvers does not necessarily localize the conduction abnormality to the HPS Subsidiary pacemakers located in the bundle of His usually show some degree of acceleration in response to exercise atropine or isoproterenol whereas pacemakers more distally located are usually only responsive to isoproterenol administration

Functional blocks

A V node In almost all patients incremental atrial pacing results in progressive prolongation of A V nodal conduction time and at higher paced rates in A V nodal Wenckebach periods and high degree A V nodal block (i e 2 1 or 3 1) This is an expected response of the A V node when the atrial rate is increased without a concomitant increase in sympathetic tone It represents a functional block because the atrial rate exceeds the capacity of the A V node to transmit impulses to the ventricle The A V block commonly associated with atrial flutter represents the clinical counterpart of this type of functional block Occasionally relatively slow atrial rates i e < 110 per minute may result in A V nodal Wenckebach phenomenon which may or may not represent abnormality The response of A V node to exercise in these patients may demonstrate capacity of the A V node to sustain 1 1 A V response at even higher rates in the presence of endogenous sympathetic stimulation which accompanies exercise

HPS Block developing within the HPS during incremental atrial pacing with continuous reliable atrial capture is an abnormal response since conduction within the HPS normally remains constant at increasing heart rates However abrupt increases in atrial rates following a long cycle length (H H interval) may result in a functional 2 1 A V block in the HPS if the first paced atrial beat reaches the HPS during its effective refractory period[33] This type of block cannot be considered abnormal at the present time and therefore it is important that events preceding the occurrence of such a block be carefully analyzed for changes in the cycle length

A V blocks due to concealed His bundle extrasystoles Closely coupled extrasystolic impulses arising from the bundle of His and concealing antegradely within the HPS (no ventricular response) as well as retrogradely within the A V node may cause conduction delay or block of subsequent sinus impulses[34] Bundle of His

recordings permit a precise diagnosis of this phenomenon.[23] Concealed bundle of His extrasystoles can cause first degree, both types of second degree, and high degree A-V blocks. The diagnosis can be suspected from long ECG rhythm strips which show, in addition to A-V blocks, junctional extrasystoles which do conduct to the ventricles with normal or aberrant QRS complexes (Fig 7).

Fig 8 illustrates the experimental production of this phenomenon. The spontaneous bundle of His extrasystole is simulated by electrically stimulating this structure at appropriate times in the cardiac cycle.[24]

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Epidemiologic evidence on the etiology of human hypertension and its possible prevention

Lot B Page, M D
Newton and Boston Mass

Primary hypertension is a major affliction of modern society affecting an estimated 15 to 20 per cent of the adult population of the United States and other industrialized nations[1,2] Nothing is known about the prevalence of hypertension in ancient times The indirect method of blood pressure measurement only became available in the early years of the twentieth century and full appreciation of the relationship of asymptomatic hypertension to major cardiovascular disease has been a product of the last few decades Spontaneous hypertension is unique to man It does not occur in animals in their native state It is not certain whether hypertension has always been prevalent or whether it is largely an abnormality of recent origin related in some way to the life patterns of modern industrialized society

It is evident that elevated arterial pressure has roots early in life There is strong evidence that both genetic and environmental factors are involved which determine whether and how steeply an individual's blood pressure will increase with age An upward gradient of blood pressure with age eventually emerges as hypertension by passing through a horizontal line arbitrarily defined as the upper limit of normal Age related trends are visible in individuals and populations within the normal range of blood pressure both in adults and in children[3] Rising blood pressure with age is a necessary prerequisite to primary hypertension and differentiates it from secondary hypertension due to endocrine, renal or renovascular disease

There is universal agreement that susceptibility to hypertension has a genetic origin although the mechanism of genetic transmission is still disputed Platt[4] has postulated inheritance through a single incompletely dominant autosomal gene Pickering[6] and others[7-9] have advanced evidence favoring polygenic inheritance as a graded characteristic

Analysis of inheritance patterns in three generations of 262 American families[10] has failed to supply clear support for either theory, but has confirmed a strong genetic influence for both hypertension and coronary heart disease and genetically associated predispositions for obesity and hyperlipidemia

Whatever the mode of inheritance the genetic influence appears to be partly if not wholly permissive Much evidence suggests that development of arterial hypertension is strongly dependent on environmental factors These factors are apparently widespread throughout the industrialized world Population studies in many parts of the world all show blood pressure rising with age and substantial prevalences of hypertension[1,2,11-15] Racial differences are also evident Non Caucasians especially American blacks show steeper age gradients and substantially higher prevalences of hypertension[16-18] than whites

Low blood pressure populations

Population studies in many parts of the world have shown that certain peoples who are outside the major Western culture are free of hyperten

From the Department of Medicine Newton-Wellesley Hospital and Tufts University School of Medicine Newton and Boston Mass
Received for publication Nov [illegible] 1975
Reprint requests Lot B Page, M D 2000 Washington St, Newton Lower Falls, Mass 02162

recordings permit a precise diagnosis of this phenomenon [3] Concealed bundle of His extrasystoles can cause first degree both types of second degree and high degree A V blocks The diagnosis can be suspected from long ECG rhythm strips which show in addition to A V blocks junctional extrasystoles which do conduct to the ventricles with normal or aberrant QRS complexes (Fig 7)

Fig 8 illustrates the experimental production of this phenomenon The spontaneous bundle of His extrasystole is simulated by electrically stimulating this structure at appropriate times in the cardiac cycle [24]

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differ in any systematic way from those who choose to remain in a traditional environment A prospective study of Polynesian migrants from Tokelau Island to New Zealand has been initiated by Prior and co workers[17] Thus far apart from small anthropometric differences the migrants appear to be representative of the population as a whole

General health

Since the low blood pressure populations of the world are without exception primitive peoples by Western standards it is reasonable to question whether their freedom from hypertension and cardiovascular disease is maintained at the cost of poor general health and malnutrition In this view their low blood pressure is an abnormality and when adequate diet and modern health care becomes available to them the normal age related increase in blood pressure is revealed Mann and colleagues emphasized the poor general health of the pygmies who showed high prevalence of splenomegaly hepatomegaly poor nutrition Kwashiorkor in children and almost universal positive treponemal serologies The Masai likewise showed a high prevalence of splenomegaly[21] Maddocks and Vines found lower blood pressure in New Guinea natives with very large spleens than in those with small spleens A similar relationship between blood pressure and splenomegaly was found among Aborigines in West Maylaysia[24]

In many of the studies of low blood pressure populations detailed information bearing on health and nutrition is lacking However Page and co workers[3] have reported findings on six Melanesian tribal societies in the Solomon Islands Detailed cultural and dietary data were obtained in each society during prolonged residence by cultural anthropologists and rank and degree of acculturation was assigned to each society based on eight separate criteria The three lowest in acculturation rank showed no rise in blood pressure with age whereas age related changes were found in the three more acculturated groups None of the six societies showed physical signs of malnutrition or protein starvation in either children or adults Hemoglobin and plasma proteins did not vary significantly over the range of acculturation and physical fitness appeared excellent in all groups judged by their ability to carry heavy loads for many miles over rough terrain Two of the low acculturation low blood pressure groups showed a high prevalence of splenomegaly while a third did not More recently Page and Moellering[4] have studied two more low blood pressure population groups living on small outlying islands in the Solomon Islands (Ulawa and Ontong Java) These people also exhibited evidence of excellent health and nutrition

Dietary change

Low blood pressure populations have been described with remarkably different diets Melanesians in New Guinea and the Solomon Islands subsist largely on root crops principally taro and sweet potato[11] The Ituri Pygmies are hunter gatherers who live on plantain berries insects rice and game[1] Kalahari bushmen have a similar diet The Masai Warrior class (or Murrans) eat only milk meat and beef blood from age 14 to age 30 [1] Polynesian groups subsist largely on coconut taro and fish,[1] and Eskimos on a chiefly carnivorous diet Change toward a more westernized diet is a universal feature of acculturation Items such as salt canned meat and fish rice wheat flour and sugar progressively supplant traditional dietary items Evidence is strong that dietary change plays an important role in inducing a change toward rising blood pressure The effect of diet probably operates through several mechanisms which are semi dependent and still poorly understood Evidence is strongest to implicate over nutrition and salt intake There is suggestive evidence to implicate other dietary items as well These factors will be considered separately

Weight gain

In long term population studies in various countries weight gain has been the most clearcut and consistent factor in predicting hypertension[2 1 1 ...] It has also been shown that lean hypertensives are more likely to gain weight than normotensives The tendency toward rising weight and blood pressure is complex and may be partly genetically linked in origin[19]

Harlan and colleagues[1] have followed a group of 1 000 white males all of whom had normal blood pressure and were at ideal weight when they entered naval flight training in 1940 In a 30

sion and show little or no tendency for blood pressure to increase with age. These low blood pressure populations represent many different racial groups, different climates, diets, customs and modes of subsistence. When comparisons are made between these populations and peoples of similar origin who have been assimilated into Western civilization, the acculturated groups have shown rising blood pressure with age and often such other biologic changes as rising serum lipids. Thus the "low blood pressure populations" are not genetically protected from rising arterial pressure. Explanation must be sought among environmental factors.

Low blood pressure populations include Chinese Aborigines, Greenland Eskimos, Melanesian tribes from several parts of New Guinea and the Solomon Islands, Polynesians from isolated islands in Fiji, Cook, Caroline and Tokelau Islands, Easter Islanders, Australian Aborigines, Nomadic tribes in Kenya, Congo Pygmies, Bushmen of the Kalahari Desert, Masai from Tanzania, West Malaysians, and South and Central American Indians from Chile, Brazil, Surinam, and Guatemala. By contrast, rising blood pressure with age, and/or clinical hypertension have been seen in town-dwelling persons from nearly all of these diverse origins.

Acculturation, or the assimilation into the dominant culture of persons from traditionally oriented primitive societies, affects nearly every aspect and facet of life. It influences religious belief, diet, moral and social values, economic status, housing, living conditions, mate selection, birth spacing, education, language, dress, daily activity, and an infinite number of other factors which impinge on each individual who undergoes the assimilation process. The process of acculturation may be slow or (more often) rapid, but appears to be an inevitable consequence of contact between a traditional culture and the forces of Western civilization. Frequently, the multiplicity of forces acting simultaneously make it impossible to determine the effect of a single factor or group of factors on biologic changes such as blood pressure trends, blood lipids, etc.

Comparisons of trends in acculturating societies with Western countries does, however, suggest that certain factors may be more or less directly involved in determining biologic changes leading toward development of hypertension and other risk factors for cardiovascular disease. Among these are general health, diet, salt intake, activity, psychosocial and psychologic stresses, occupation, and family size. Many of these factors are inter-dependent, or at least only semi-independent, and some are clearly more potent than others.

Acculturation

A number of studies have demonstrated that the totality of changes which occur when primitive people become town dwellers or migrate to an alien and more westernized environment sharply affect blood pressure trends. Maddocks[2] reported that three populations of New Guinea natives from widely separated areas all showed blood pressure falling with age. By contrast, the acculturated residents of Hanuabada, on the outskirts of Port Moresby, showed blood pressure rising with age. Cruz-Coke and colleagues[8] showed virtually no rise in blood pressure with age among Easter Islanders who remained on the island, whereas a steep rise occurred among migrants who had lived on the mainland for three to five years in the "stormy environment of a low income group in a rising Latin American country." Cruz-Coke and associates[33] have also studied a population of Aymara-speaking Chileans who are genetically homogeneous but live in a sharply divided ecosystem.[33] In the less acculturated highland Chileans, blood pressure did not rise with age, whereas both systolic and diastolic pressures increased with age in their lowland relatives who used more advanced agricultural methods and were subjected to nearby urban pressures. Similar trends were noted in two neighboring Indian tribes in Brazil by Lowenstein,[34] and in Guatemala by Hoobler and associates.[3]

Several independent studies among similar, but not identical population samples along the shores of Lake Victoria in Africa suggest a progressive blood pressure trend over a 40-year period. Donnison[39] in 1929, found blood pressure falling with age. Williams[40] in 1941 found pressures neither rising nor falling and Shaper and Saxton (1969)[41] found pressure rising among people in this area as steeply as in the industrialized countries.

In considering the effects of migration, it is important to determine whether the migrants

Their traditional diet of meat milk and blood contains 2 to 3 Gm of sodium per day The Army ration is high in carbohydrate and provides an average of 16 grams of sodium per day During the first year in the Army body weight and skinfold thickness of the Samburu recruits increased but blood pressure remained unchanged In the second and third years weight and skinfold values diminished but blood pressure increased progressively Further changes following discharge and return to tribal life have not been reported

Once hypertension becomes established a quantitative effect on blood pressure is seen only at extremely high or low levels of intake Indeed clinical experience shows that moderate variation in salt intake has little effect on established hypertension

Taken as a whole the evidence that excessive salt intake is a highly important factor in the induction of age related increase in blood pressure in genetically susceptible young individuals seems very persuasive and worthy of more attention than it has thus far received as a potential mode of intervention in the prevention of clinical hypertension

Other dietary factors

Blood pressure tends to be higher in rural than in urban populations in United States[60, 6] England and Jamaica A socioeconomic trend has also been noted with progressively higher pressures in groups from lower socioeconomic brackets Although a psychosocial influence immediately suggests itself the studies of Langford and associates[60, 6] suggest a possible dietary explanation In Langford s studies the blood pressure difference is not explained by differences in sodium intake However significant differences in sodium to calcium and sodium to potassium ratios are found in the urine of subjects from lower socioeconomic and rural areas These findings suggest that high potassium and/or calcium intake may exert a protective effect on the effects of high salt intake and the absence of this protection may influence the observed differences High potassium has been shown to partially protect salt sensitive rats from the effects of salt excess and high calcium intake promotes sodium excretion[6] Further work is needed in this area

Hypertension and cardiovascular disease have been reported to be more prevalent in areas with soft than with hard drinking water[68, 69] although this has not been universally confirmed[70] More study is needed in these areas as well

Psychosocial and racial factors

Higher blood pressure at all ages and substantially greater prevalence of hypertension have been found in blacks than in Caucasians in United States[1, 1, 1] It is probable that this is at least partly explained by genetic factors[11] However a gradient in blood pressure has been found in relation to socioeconomic status for both blacks and whites (see above) with lowest pressures in the highest socioeconomic status and highest pressures in poorest rural groups[60] This gradient is sufficiently marked to obliterate racial differences when urban blacks of the upper socioeconomic bracket are compared with poor rural whites Both psychosocial and dietary explanations have been offered to explain these differences

Many investigators have speculated concerning psychologic and psychosocial factors in the genesis of hypertension with generally inconclusive results[1, 13] Henry and Cassel[1] have adduced evidence from a wide variety of sources in support of a theory that rise in blood pressure develops when aging persons find themselves in a social milieu in which ethical and moral values learned in childhood are no longer supported While intuitively attractive hypotheses such as this are hard to test rigorously Studies of indices of anxiety[4] and occupation[73] have yielded conflicting results Effects of meditation[75] on blood pressure appear to have only small and transient effects

A relationship of blood pressure to family size has been noted in several parts of the world[1, 6] with blood pressure diminishing as number of family members increases Although there is no obvious explanation for this it is of note that among Zulus in South Africa who are under intense economic and social stresses the reverse is true[79] In addition the urban-rural trend is reversed with higher pressures in large families and in the urban compounds

In general the psychosocial influences on blood pressure trends have been inconsistent and difficult to delineate They are probably variable in importance in different cultural settings and with probable exceptions are more influential on

year follow up study is gain in weight between age 24 and 36 strongly predicted rising blood pressure which continued upward from age 36 onward regardless of subsequent weight change Change in weight in this and other studies[17, 48] is distinctly more strongly correlated with rising blood pressure than initial weight or obesity In industrialized societies, mean weight tends to rise with age This is not true in primitive societies, where weight remains level or falls with age[25, 50] Acculturation is however, usually associated with rising weight, and it is difficult to separate this effect from other influences of changed diet and activity This effect has been noted in Polynesians[25] New Guinea Melanesians [2] and Guatemalan Indians[51] although the weight changes in these acculturating groups is small by comparison with the increases seen in the United States

Salt intake

For many years, it has been suspected that excess salt may induce hypertension in genetically susceptible individuals[21] By selective inbreeding Dahl and co workers[31, 52] have clearly demonstrated interaction between salt intake and genetic susceptibility to hypertension in rats They have also shown a roughly linear relationship between average daily salt intake and the prevalence of hypertension in several populations in different parts of the world[31] On the other hand investigation of salt intake within populations has consistently failed to show any significant relationship between salt intake and blood pressure of individuals[25, 33, 53]

Examination of available data on sodium intake and excretion obtained on low blood pressure populations reveals the striking fact that low sodium intake is a universal finding in all such populations whenever and wherever it has been measured Statements to the contrary[21] have been unsupported by data and apparently are based on the assumption that the availability of salt as in coastal people is necessarily associated with salt ingestion Natives of Ontong Java Atoll in the Solomon Islands live in intimate contact with the sea, yet avoid use of salt and excrete little sodium in the urine[42] Strikingly high plasma renin activity in this population sample also reflects low sodium intake Blood pressures in Ontong Java remain low throughout life[43] Coastal Eskimos are also reported to avoid salt[31]

Acculturation, with use of Western dietary items invariably appears to lead to increased salt intake In a study of six Solomon Islands populations Page and associates[11] found blood pressure rising with age in females of the three more acculturated societies, but not in the three less acculturated Blood pressure trends were best correlated with salt intake All six societies were at low levels of acculturation by Western standards, and weight decreased with age in all Highest blood pressures were found at all ages and both sexes among a group (third out of six in rank of acculturation) who boiled their vegetables in sea water and had by far the highest salt intake of the six groups Prior and associates[25] also found a significant relationship between blood pressure change and salt intake in comparing two Polynesian populations and a similar relationship was noted by Lowenstein[34] in comparing Indian populations in Brazil Although firm data are not available substantial changes in use of salt appear to be temporally correlated with rising blood pressure in parts of Africa[34] and among Indians of the Southwestern United States[5]

Extremely high salt intake may partially explain the high prevalence of hypertension among farmers of Northern Honshu Japan,[58] and coastal fishing villages of Newfoundland[59] It has not been found possible to explain differences in blood pressure between black and white populations in the United States[60, 61] The failure to find correlation of blood pressure and salt intake within populations should not be surprising in a heterogeneous population with widely differing genetic susceptibility all members of which ingest moderately large amounts of salt Salt excess may exert its greatest influence by initiating age related blood pressure trends in infancy and early childhood as it does in the salt susceptible rat

Excessive salt intake has not been shown to have an immediate effect either in the salt sensitive rat or in man[5] In animals salt excess induces a change in arterial pressure which is delayed in expression and which once established is progressive[32] In man, it is difficult to find a model which corresponds to the long term experiments in animals Perhaps the closest approximation is the report of Shaper and colleagues[62] on nomadic Samburu warriors from Northern Kenya who served for several years in the Army These men belong to a population which shows no rise of blood pressure with age[50]

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short term than on long term blood pressure trends

Conclusions and practical considerations

Primary hypertension, a major precursor to arteriosclerotic cardiovascular disease throughout the industrialized world, may be an abnormality of relatively recent times In many pre industrial populations it is totally absent, and its precursor an age related rise in blood pressure is also absent in many of these same populations Many studies show that acculturation' rapidly results in the appearance of upward trends in blood pressure Genetic predisposition to rising blood pressure is a prerequisite to primary hypertension and is widespread in all races and climates However environmental factors are also necessary for this hereditary susceptibility to express itself Both major and minor factors may be involved in the induction of age related blood pressure increases Major factors include weight gain with age and intake of salt in considerable excess of physiological needs Race general health and nutrition and the ratio of dietary sodium to other electrolytes and minerals may also be important

Factors of somewhat lesser importance may also influence long term trends in blood pressure These include family size and various socioeconomic and psychosocial influences

At present great emphasis is being placed on the detection and treatment of established hypertension However upward trends in blood pressure are evident long before they reach hypertensive levels Evidence reviewed here suggests that by avoidance or elimination of major factors known to induce these trends clinical primary hypertension may be a preventable disease

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Annotations

Lutembacher syndrome obsolete? A new modified concept of mitral valve disease and left-to-right shunt at the atrial level

Lutembacher drew special attention in 1916 to the association of mitral stenosis and atrial septal defect, giving the first comprehensive description of the syndrome Initially the mitral stenosis was thought to be congenital however it was subsequently proved to be rheumatic in origin. In the past few years several communications [1] reported other pathological abnormalities of the mitral valve apparatus beside pure mitral stenosis In view of these observations we propose that the present concept of Lutembacher syndrome as it is limited to atrial septal defect and mitral stenosis should be abandoned A new enlarged concept based on the basic pathology of the mitral valve independently on the level of the atrial left to-right shunt should be entertained, excluding patients with ostium primum defects. This new concept comprises patients with different hemodynamics.

Group A. This group includes those patients previously included in the initial Lutembacher description Pure mitral stenosis or combined mitral stenosis and insufficiency or additional valvular involvement and a left to right shunt This includes those patients with partial anomalous venous drainage and intact atrial septum since the basic pathophysiology of the syndrome—decompression of the left atrium whose outlet is obstructed—can be created by the two different anomalies causing left-to-right shunt at the atrial level. The hemodynamic changes in this group of patients have been reported and the difficulties in diagnosing the mitral stenosis are known however obvious gradient across the mitral valve and absent diastasis in the left atrial pressure curve are suggestive

Group B In this group of patients are included those in whom mitral insufficiency is the only valvular lesion This category includes rheumatic mitral insufficiency ostium secundum defect and a cleft of the mitral valve or balloon mitral valve ruptured chordae tendinae myxomatous degeneration of the mitral valve and those recently reported patients with clinical and hemodynamic mitral incompetence due to prolapse of the posterior leaflets of the mitral valve and ostium secundum defects. Usually the mitral insufficiency does not cause diagnostic difficulties however the correct anatomic diagnosis is established at surgery or angiographically

From the hemodynamic point of view the mitral incompetence does not present problems since it is well reflected in the cineangiographic studies although the regurgitant flow is not always reflected in the wedge or right atrial pressure curves absent large "V" waves in the left atrial pressure tracings do not rule out mitral regurgitation

This modified concept gives a better understanding of the underlying mitral valve pathology in patients with a left-to-right shunt at the atrial level, and provides a sound approach to the clinical and hemodynamic diagnosis and proper treatment of the valve abnormalities This concept would also imply that every patient with a left-to-right shunt at the atrial level should have a left ventriculogram prior to surgery to determine the state of the mitral valve furthermore the importance of recognizing clinically silent or evident mitral regurgitation is emphasized by the clinical course in some of these patients. When the diagnosis of mitral valve pathology is established bacterial prophylaxis should be advised

M Gueron M.D
J Gussarsky M.D
Kupat Holim Health Insurance Institution of the General Federation of Labour in Eretz Israel
Cardiopulmonary Laboratory
The Negev Central Hospital
Beersheba Israel

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Beta blockade and coronary circulation

Numerous articles have documented the usefulness of beta blockade in the treatment of patients with angina pectoris. The relief of pain is usually attributed to the reduction of myocardial oxygen consumption consequent to a decrease in contractility and heart rate. Reduction of the systemic pressure in the long term treatment of hypertensive patients with angina also plays a role. Adverse hemodynamic effects of beta blockade are the increase in heart volume enhancing the left ventricular wall tension and the rather frequently observed increase of left ventricular end-diastolic pressure reducing the perfusion gradient across the myocardium. In this balance between oxygen saving and demanding effects the behavior of the coronary blood flow is of importance.

Measurements of total coronary flow in experimental settings during beta blockade induced by propranolol have revealed a reduction which has been roughly proportional to the decrease in myocardial oxygen consumption either directly measured or derived by hemodynamic indices. The coronary vascular resistance has been found to increase correspondingly. Two alternative explanations for these changes are readily at hand: (1) coronary flow is decreased as an adjustment to decreased oxygen demand and (2) coronary vasoconstriction due to unopposed alpha receptor activity is reducing the flow. Attempts to solve this problem have been made by utilizing bypassed canine hearts.[4] In this preparation the perfusion pressure can be controlled and the left ventricle performs little work. Suggestive evidence has been afforded in favor of direct vasoconstriction under beta blockade by propranolol and related compounds.

The effects in man and more importantly the effects of beta blockade on the regional distribution of the coronary flow have recently been reviewed. In brief there is suggestive evidence that propranolol favorably alters the myocardial flow distribution between ischemic and nonischemic areas. Especially the perfusion of the sensitive subendocardial regions is preserved in ischemia at the expense of the less vulnerable subepicardial layers.

This communication briefly portrays new experimental data obtained in guinea pig hearts utilizing a new technic allowing the assessment of myocardial blood content in different phases of the cardiac cycle.[7,8] The essential part of the method is an electrically triggered device cutting a transmural myocardial biopsy and throwing it in less than 0.02 second into isopentane cooled by liquid nitrogen. I[131] was used to label the plasma. Propranolol in a dose of 0.1 mg per kilogram of body weight markedly reduced the subepicardial blood content in all measured phases of the cardiac cycle. In subendocardium the reduction was less, resulting in a decreased subepicardial/subendocardial ratio. Increase of the dose of propranolol to 1 mg per kilogram of body weight did not greatly modify the response. Practolol in a dose of 0.3 mg per kilogram of body weight did not change the subepicardial blood content. The same was true for the subendocardium except in late systole when the blood content was higher than the control value. Increasing of the dose of practolol to 6 mg per kilogram of body weight resulted in decreased subepicardial blood content in early systole and end-diastole. The subendocardial values also decreased significantly in peak systole and end-diastole. The heart rate decreased in these experiments from about 265 to about 215 per minute. There was no difference in the heart rate decrement between propranolol and practolol.

These data are in agreement with the previous experimental findings on propranolol both as regards the total coronary flow and the subepicardial/subendocardial distribution. The data on practolol support the earlier unexpected finding of increased coronary blood flow in dogs after practolol. The momentary myocardial blood content reflects the extent of the vasculature involved in any given experimental situation and when determined in different phases of the cardiac cycle it showed the long known fact that coronary flow is highly phasic. Propranolol caused the greatest reduction in end diastole presumably due to increase in end-diastolic pressure and in general smoothed out the phase differences in the myocardial blood content. The deviating effect of practolol may be due to the intrinsic sympathomimetic properties of the compound, but the decrease in heart rate similar in magnitude to that after propranolol speaks against this reasoning. The effect of propranolol was also studied after coronary ligation. In this situation the blood content of the ischemic myocardium was not changed and also the ratio of subepicardial/subendocardial blood content remained constant. This finding does not support the earlier data obtained by radioactive microspheres but suggests that the vasodilatation caused by ischemia is not modified by propranolol in guinea pig hearts.

Direct extrapolations from these data to man are not possible but neither are technics for subendocardial versus subepicardial flow measurements in intact man yet available. Meanwhile these and earlier experimental data are useful in influencing our thinking and the selection of therapeutic interventions in human coronary heart disease.

M. H. Frick, M.D., F.A.C.C., F.C.C.P.
K. S. Virtanen, M.D.
Cardiovascular Laboratory
First Department of Medicine
University Central Hospital
Haartmaninkatu 4
00290 Helsinki 29
Finland

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Coronary care units

It is widely assumed that treatment in coronary care units after a myocardial infarction confers great benefits on patients and every effort is made to improve notification and transfer to hospital. Yet proof of this does not measure up to the high standards demanded for other forms of treatment as, for example in the assessment of new drugs

The evidence from randomized cases in the Bristol Survey showed that it was better for some patients to be kept at home Unfortunately only 28 per cent of cases were randomized and most of these came under care after the period of highest mortality had past More recently a total community survey in Cleveland England (Population 400 000) has shown fatality rates, when standardized for age and sex to be the same whether patients were treated at home in general wards or in coronary care units The study was made over a period of one year and included almost 2 000 cases of myocardial infarction So far as could be determined the patients in the three groups did not differ greatly in severity Thirty four per cent of patients were treated at home 36 per cent in wards, and 30 per cent in coronary care units No attempt was made during the survey to alter doctors usual methods of treatment. The study was designed to determine the care already being provided for patients after myocardial infarction and how effective it was in order to plan a community service for the future The median time for patients coming under care three hours, did not differ greatly in the three groups

The general practitioner is usually the first doctor to be called to patients and with this kind of evidence he is becoming preoccupied with the question "Home or hospital?" Even those who are convinced that there is a place for home care are apprehensive about taking such responsibility and seek advice on the best treatment to give to patients they see in the home—both for those they continue to treat at home and those they send to hospital. Unfortunately hospital physicians find it difficult to detach themselves from the coronary care unit situation and to prescribe guidelines for primary care. The manner in which hospital and community medicine are divorced from one another in the United Kingdom may in part be responsible for this.

It is becoming apparent that general practitioners must learn to give primary care of high quality whether they subsequently admit their patients to hospital or not Adequate relief of pain and the treatment of many dysrhythmias are within their competence in the home and it is believed that these measures alone may well diminish the extent of permanent myocardial damage An attempt has been made to give general practitioners guidelines for this approach. It assumes that the general practitioner possesses a cardiograph and is familiar with a few drugs appropriate to coronary care Despite the misgivings of cardiologists about general practitioners using cardiographs, the new generation of primary physicians expects to include them as tools of their trade and it is only a matter of time before they become the rule

A general practitioner caring for 3 000 patients will have about 15 cases each year in his practice Some will be found dead or die before help could possibly arrive The time of greatest mortality is in the first hour or two but at present the general practitioner will only be called during this period on about two occasions a year The guidelines arbitrarily distinguish the treatment of patients who are seen within two hours of the attack from that given to those the doctor is called to later There is extreme urgency in reaching the early group and the general practitioner must be prepared to keep patients under supervision during this critical period Movement to hospital is undesirable unless the patient is stable and good transfer facilities are available He can monitor the patient by the sight or sound of the cardiograph, without using paper Simple monitors and defibrillators are being produced but they are still relatively expensive A single physician may not feel justified in possessing them but a larger group might consider them worthwhile Indeed it would seem logical to encourage the formation of groups of general practitioners who would undertake special training in resuscitation techniques and be provided with the necessary equipment by the community There is evidence that such teams could reach patients much more quickly than coronary ambulances

Two hours may seem a long time but much of this time will be absorbed by the delay in the doctor being called by travelling in establishing a diagnosis and in relieving pain At a point about two hours from the onset of the attack the general practitioner must decide whether to continue home care or transfer the patient to hospital If the patient is stable and has someone to care for him then on present evidence home care is probably justified If the patient is unstable or has some disorder of conduction such as a heart block then transfer to hospital will be essential but should be done under

medical supervision and with adequate monitoring and resuscitation facilities

In most cases of myocardial infarction however the general practitioner will be called after the time of greatest mortality Evidence is accumulating that these patients do equally well at home despite the claims of those who point to the lives being saved by resuscitative techniques Admission to hospital may be necessary only on social grounds or when there is a persistent medical complication such as unstable rhythm or disorder of conduction

Home care and hospital care should be seen to be complementary and not as alternatives Each community should develop its own system for the care of patients after myocardial infarction in which general practitioners should play an important role It should not be totally hospital orientated—home care transfer facilities and hospital care should all be considered together With present knowledge and a little guidance and encouragement the general practitioner could play his part in the coronary care team Simple resuscitation equipment is becoming available and local groups could be trained in its use Hospital admission will be needed for some cases but only on well-defined criteria If emphasis is placed on such a community concept of treatment then the correct balance of care is more likely to be achieved and appropriate training will be given to those who need it.

A Colling M.D., F R C G P
A W Dellipiani M.D F R C.P
P McCormack M.R C.P
Cleveland County England

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Of URI and cardiomyopathy

As indicated many years ago infections comprise one of the most common causes of heart disease This fact is frequently ignored because physicians and cardiologists seem to be consulted and confronted with management of heart disease at relatively late stages Therefore prevention early diagnosis and early treatment are too frequently neglected Yet if prevention of heart disease and reduction of death rate from heart disease are to receive major emphasis preventive measures and early treatment are of paramount importance

Cardiomyopathy is a common type of heart disease Unfortunately cardiomyopathies are not recognized until the hemodynamic stages and manifestations of congestion restriction and obstruction are already present These diseases at one time had a beginning—a time when the myocardial disease was early mild or only potentially present For example viral and even bacterial infections frequently produce cardiomyopathy The time to treat viral cardiomyopathy therefore is at the time of the viral infection usually an upper respiratory tract infection (URI) at its onset and if possible before the heart is injured Changes in the ST segments and T waves of the electrocardiogram may be noted (when sought for) as the earliest manifestations of myocardial damage sustained at the time of infection Patients with such changes should be placed at complete bed rest and certainly must avoid active physical and mental stress, and should be carefully watched by simple conventional clinical and laboratory examinations e g history taking physical examination electrocardiogram and x rays *Who is to know who will* develop cardiomyopathy following a URI? It is advisable to remember that during an infection the potential state for myocardial damage exists Therefore study the patient while being pragmatic in his management at the same time Any viral URI or viral pneumonia is a potential etiologic factor for viral myocarditis valvulitis and pericarditis with possible initiation of a typical or atypical cardiomyopathy Surely with these ideas in mind early diagnosis and early proper treatment of the infection introduction of preventive measures and early treatment of the heart disease if it is already present cannot be overemphasized whenever a viral infection exists and potential viral cardiomyopathy likewise exists

George E Burch M D
Tulane University School
of Medicine and Charity Hospital
New Orleans La 70112

REFERENCE

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Letters to the Editor

Positive and negative distribution volumes

To the Editor

In the February 1975 issue of AMERICAN HEART JOURNAL, Drs Hoffman Rosen and Wit discuss clinical pharmacologic considerations in the administration of antiarrhythmic agents They state that the apparent volume of distribution is the plasma concentration divided by the dose

$$\frac{mg/ml}{mg} = ml$$

This would not express ml but ml. The apparent volume of distribution is actually calculated by dividing the dose by the plasma concentration

$$\frac{mg}{mg/ml} = ml$$

William H Jeffery Pharm D
Assistant Professor of
Pharmacy (Clinical)
College of Pharmacy
The University of New Mexico
Albuquerque N M 87131

REFERENCE

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Reply

To the Editor

We wish to thank Dr Jeffery for bringing to our attention this typographical error on our part As he correctly points out

$$AVD = \frac{mg}{mg./ml.} = ml$$

Brian F Hoffman M.D
Michael R Rosen M.D
Andrew L Wit Ph.D
D pt of Pharmacology
College of Physicians and Surgeons
Columbia University
630 W 168th St
New York N Y 1003?

Repetitive supraventricular tachycardia out of context

To the Editor

The term "repetitive tachycardia" was coined by Parkinson and Papp with a specific connotation and precise definition recurrent paroxysms are the rule and normal rhythm is the exception the difficulty now is to obtain a normal electrocardiogram" Thus, the term applies to a rare condition with an almost continuous presence of ectopic rhythm frequently interrupted by brief periods of sinus rhythm This term has been used since in this connotation

The authors of the editorial "Repetitive supraventricular tachycardia in context"[2] really meant not *repetitive* but *recurrent tachycardia* There is enough confusion in cardiac terminology already and one would hope that terms would be used in their original meaning rather than loosely

Arthur Selzer M D
Division of Cardiology
Presbyterian Hospital of
Pacific Medical Center
Buchanan and Clay Streets
San Francisco Calif 94115

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Criteria for the LGL syndrome

To the Editor

In your Editorial article for August last year (AM HEART J 90 131 1975) Castellanos and Myerburg argue for new criteria for the LGL syndrome I do agree with them but for different reasons

In the original article Lown Ganong and Levine describe the syndrome of short P R interval, normal QRS complex and paroxysmal rapid heart action"[1] They did not have ECG records of the tachycardia in all patients The definition does not distinguish between ventricular and supraventricular tachycardia One of my patients had P R interval of 0 11 sec and paroxysmal ventricular tachycardia. Careful examination revealed no other abnormalities. This patient s manifestations corresponded to the definition given of the LGL syndrome

Some authors describe a syndrome" of short P R interval and normal QRS complexes as the LGL syndrome They have forgotten the tachycardia which is the "sine qua non" of the LGL syndrome They do in fact describe a part of the normal population wherein the LGL syndrome appears

Others do not agree that the P R interval is to be 0 12 sec or less The term short P R interval" seems not to be clearly defined.

In recent years sexual and racial differences in the duration of the P R interval have been noted. The duration of the intervals is then of limited value without reference to race and sex.

The LGL syndrome is today interpreted as AV nodal re-

entry tachycardia in persons with incomplete AV nodal bypass Why not just call it so?

Pal Moller M D
Fylkesjukehuset i Odda
Medical Department
5751 Odda
Norway

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Reply

To the Editor

Dr Selzer's concern about etymologies is not new It is found in Genesis 17 15 in reference to the changing of the name Abram to Abraham and Sarai to Sarah Twenty two centuries ago the sophists in Athens carried semantic arguments to such extremes that Plato stated that serious etymologic discussions usually led nowhere

This is due to the fact that every user thinks that his term is the best And after all this is not an easy matter for what makes a name ? Is it the one given by the first person who described the object or the phenomenon? Or is it popular usage?

We cannot believe that Dr Selzer implies that the words repetitive" and recurrent have a different meaning Apparently he considers that the arrhythmia called repetitive tachycardia was first described by Parkinson and Papp in 1947 and that this term is now universally accepted Not so Gallavardin had previously called it extrasystolie a centre excitable (1922) or tachycardie en salves (1924) Coumel has repeatedly referred to this arrhythmia as permanent" (or chronic) tachycardia

We borrowed the term repetitive tachycardia from Scherf and Schott who are well known authorities in the field These authors used it in reference to repetitive reciprocating A V tachycardia This nomenclature was followed in the light of recently acquired specialized electrophysiological information and with due respect for their lifetime work and in depth knowledge

Dr Möller as well as ourselves referred to the Lown Ganong Levine syndrome mainly because of usage Actually this entity was initially described by Clerc Levy and Cristesco in 1938 Burch and Kimball first considered that this syndrome could be due to the presence of an atrio His bundle pathway At present most authors (see critical review by Narula) consider that in all probabilities the short P R interval is due to the functional presence of the atrio-nodal (partial) bypass described by James in 1961 or of the atrio His bundle type observed by Brechenmacher and associates in 1974 This was supported by our studies performed in 1971 in which a short A H interval was found However in an isolated study Mandel and co workers reported three cases in which the H V (not the A H) interval was short Variants (?) of this syndrome occur when there is coexisting organic heart disease For instance the P R interval might be normal in patients with intra atrial conduction defects (producing P A prolongation) or His Purkinje delays (resulting in increased H V intervals) Thus the entity under consideration is best characterized (from the clinical side) by the presence of repetitive (or recurrent) supraventricular tachycardias and (from the dynamic electrophysiological viewpoint) by the abnormal response of the A H interval to atrial pacing at increasing rates and to the extrastimulus method

Agustin Castellanos M D
Robert J Myerburg M D
University of Miami School of Medicine
P O Box 520875
Biscayne Annex
Miami Fla 33152

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Book reviews

Ultrasonic Techniques in Angiology By D E Strandness Jr M D and D S Sumner M D Vienna 1975 Hans Huber Publishers 146 pages

This small paperback describes the standard methods and technics used in ultrasonic clinical angiology Technology and apparatus are described It is obvious that the skill of the operator is most important The authors describe the application of ultrasonic diagnostic procedures for the study of the arterial and venous systems to detect thrombolic lesions changes in the rates of arterial and venous blood flow and even abnormal function of venous valves The velocity detector for example can be used to locate the sites of arterial and venous occlusion in large and medium size vessels The method employed with the velocity detector is described The detector already has use in clinical practice and will be further developed as experience with it and the apparatus is improved This is a very useful book It should interest cardiologists cardiovascular surgeons and those interested in the peripheral circulation This book is well written and is practical

The Peripheral Arterial Chemoreceptors Edited by M J Purves London 1975 Cambridge University Press 492 pages Price $39 50

This book contains the papers and discussions presented at an international workshop held in Bristol in 1973 The importance of peripheral arterial chemoreceptors is well known Recent interest in these and related chemoreceptors has increased considerably and the advances in knowledge have been great The publications have been too numerous for anyone to follow closely This book summarizes the present state of knowledge in many short papers by many internationally well known contributors Sections include discussions of ultrastructure of cells concerned with chemoreception histochemistry and neurophysiology of the carotid body reflex pathways and chemoreflexes and their metabolic activity The discussions are as usual very provocative The book should interest physiologists and pharmacologists whereas cardiologists and other clinicians who have not followed the subject closely will find the presentations difficult to understand but important to know in order to appreciate fully the physiology of the circulation This is an important and good publication

Vectorcardiography 2nd edition By Louis Lemberg M D and Agustin Castellanos Jr M D New York 1975 Appleton Century Crofts Inc 260 pages Price $16 00

This second edition on vectorcardiography is essentially a self teaching manual The reader is expected to learn the fundamentals of clinical vectorcardiography by careful study of simple diagrams and recordings of the vectorcardiogram and electrocardiogram This approach is a good one but the reader is warned to read this manual carefully because of careless writing For example at the outset on page 1 the authors state that the sense of a vector is defined by the direction in which it points This is so but on page 2 they say the head is positive and the tail is negative This is not so under all circumstances for both the tail and head can be either negative at the same time or positive at the same time This example and other statements are not correct or clearly indicated Oversimplification can lead to erroneous discussions Readers will find the manual useful Readers should review vector mathematics and electrophysiology in order to use this manual properly The authors use abbreviations excessively throughout which tends to delay learning and cause confusion

Actualites Cardio-vasculaires Medico Chirurgicales Edited by A Gonin P Michaud A Perrin and J Descotes Paris 1975 Masson & Cie Editeurs 216 pages

This book in French on angina pectoris reviews the medical and surgical management of ischemic heart disease due primarily to arteriosclerosis of the coronary arteries The concepts reflect mainly French and Canadian studies and practices The views on medical and surgical management are clearly indicated and are compared with that of the rest of the world This reviewer finds the concepts results and opinions to be essentially the same as that from other affluent nations This book is well organized and well written It is a good book for a review of angina pectoris

Heart Disease Edited by Earl N Silber M D and Louis N Katz M D New York 1975 Macmillan Publishing Co Inc 1 430 pages

This is an excellent textbook of cardiology Silber has written practically the entire book himself The number of contributors is small It is written for the practicing clinician The physiologic pathologic and electrocardiographic aspects of cardiology are presented from the clinical points of view The section on heart disease is clinically oriented The book is organized for the physician and in the usual fashion found in textbooks in medicine The bibliographies are well chosen This is a very good textbook of cardiology It is easy to read and quite encyclopedic Unfortunately Dr Louis Katz is not alive to see the completed book

Drugs in Cardiology Part 1 Edited by Ephraim Donoso M D New York 1975 Stratton Intercontinental Medical Book Corporation 239 pages Price $24 75

This is a practical clinical publication on the common drugs for therapeutic problems in cardiology The thirty contributors are in the practice of cardiology and are therefore aware of the indications and contraindications of drugs in management of various heart diseases The various discussions include procainamide quinidine lidocaine and other antiarrhythmic agents Atropine nitrites beta blocking agents are among the many other drugs discussed The indications dosage and other therapeutic principles are reviewed This book should interest all doctors but especially general practitioners and internists The book is worth owning for study and reference

The Pharmacologic Basis of Therapeutics Edited by Louis S Goodman and Alfred Gilman New York 1975 MacMillan Publishing Company Inc 1618 pages Price $30 00

The fifth edition of Goodman and Gilman s book The Pharmacologic Basis of Therapeutics is still a great text This publication is authoritative and a classic The authors keep it up to date This edition continues to be clearly written comprehensive and is an excellent source of extremely useful

information Every physician would profit immensely if he had a copy in his library for ready reference The book is written for practicing physicians. The section on chemo therapy of microbial disease for example should assist physicians greatly since the use of antibiotics offers difficulties in the daily practice of medicine and is so arbitrary in practice by many doctors. The fifth edition is an excellent publication

Books received

Hematological Compl cations in *Card ac Practice* Edited by Joanne [illegible] Jepson M D and William S Frankl M D Philadelphia 1975 W [illegible] Saunders Company 293 pages. Price $.,8 00

Smoking and *Its Effects on Health* World Health Organization Technical Report Series 1975 No 568 Geneva, 1975 World Health Organization 100 pp Price 9 Swiss francs

Malpract ce and You By John Barchilon M D New York, 1975 Ace Books 259 pp Price $1 75

Kliniktaschenbucher—Notfall EKG—*Fibel* By G G Belz and M Stauch Berlin W Germany 1975 Springer Verlag 87 pp Price $7.30

Kliniktaschenbucher—*Leitfaden fur den Klinischen Assistenten* By G Friese and A Völcker Berlin W Germany 1975 Springer Verlag 159 pp Price [illegible] 60

Your Second Life By Harold L. Karpman M D and Sam Locke Los Angeles 19 5 J P Tarcher Inc 2"0 pp Price $8 95

Progress in Chemical Fibrinolysis and Thrombolysis Edited by John F Davidson M.B Meyer M Samama M D., and Pierre C Desnoyers Sc.D., New York 19/5 Raven Press 306 pp Price $26 00

Announcements

Symposium on pediatric nephrology

A symposium on pediatric nephrology will be sponsored by Georgetown University and the San Juan City Hospital at the Caribe Hilton Hotel San Juan Puerto Rico May 12 through 15 1976 Topics include Glomerulopathies Tubular Disorders Urinary Tract Infections Hypertension Hormones and the Kidney and Renal Failure Speakers are internationally known in the field of nephrology Accreditation in Category I for the Physician s Recognition Award of the AMA has been applied for Tuition $150 for physicians in practice $75 for physicians in training (with letter from chief of service)

For information write Jose F Pascual M D P O Box 3342 Old San Juan Puerto Rico 00904

Advances in cardiac pacing

A conference entitled Advances in Cardiac Pacing will be held at the University of Michigan Medical Center May 13 and 14 1976 The conference will review basic concepts and indications for temporary and permanent cardiac pacing as well as explore the problems in long term evaluation of the pacemaker patient Workshops and an evening of small group discussions are planned to allow adequate opportunity for the discussion of problems and issues of special interest to course registrants.

For further information please contact Robert K Richards Ph D Office of Continuing Education G 1109 Towsley Center University of Michigan Medical Center Ann Arbor Mich 48109 Telephone (313) 764 2287

Fifth Annual Cardiology Symposium

The Johns Hopkins Medical Institutions will sponsor the Fifth Annual Cardiology Symposium on June 10 through 12 1976 The topic for the symposium will be Cardiology for the Internist—Clinical Problem Solving

For further information please contact Dr J O Neal Humphries or Dr Bertram Pitt Carnegie 568 The Johns Hopkins Hospital Baltimore Md 21205

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Editorial

Observations on the diagnosis of isolated rheumatic carditis

C Ward MD MRCP*
Sheffield England

Rheumatic fever would be unimportant if it were neither accompanied by acute carditis nor followed by chronic rheumatic heart disease In fact rheumatic fever is generally accepted as the only *significant* cause of acute and chronic acquired valvular disease—even when a rheumatic history is lacking This concept encouraged by Cheadle's exposition of a *spectrum of rheumatic carditis* was firmly established by the classical studies of Coombs (1924) and Findlay (1931) Coombs claimed that all *acquired mitral* valve disease (and all unexplained cardiomegaly in children) was rheumatic because *no alternative theory of causation is available* and this forms the basis of the currently accepted view of the pathogenesis of valvular heart disease

This view has been challenged by the suggestion that viruses may also cause valvular heart disease —a suggestion supported by experimental studies by clinical descriptions of *the development of* valvular murmurs in patients with proved virus infections and by the demonstration of virus antigen in the myocardium and endocardium of patients with acquired valvular disease[7] This suggested role of viruses is not generally accepted the traditional explanation is still *considered adequate* There are however striking similarities between cases of viral myopericarditis and certain categories of isolated rheumatic carditis a reappraisal of the criteria used for the diagnosis of rheumatic fever is therefore justified to determine if these criteria adequately distinguish between the two forms of carditis (rheumatic and viral)

The accepted concept of a disease can be defined on the basis of the criteria used for its diagnosis However if the criteria are too lax, cases may be included which have some other etiology and consequently an inaccurate concept of the disease in question will be perpetuated The evidence presented below suggests that this has happened in the case of rheumatic carditis

The fundamental problem which is involved in diagnosing rheumatic fever and the accepted approach to its solution are summarized in the introduction to the revised Jones criteria There is no single laboratory test symptom or sign which is pathognomonic of the disease although several combinations of them are diagnostic[*]

In situations where a specific diagnostic test is available cases which do not comply can be excluded and borderline cases can be identified When there is no specific test diagnosis is *more* subjective and depends to some extent on the individual clinician's concept of the disease spectrum involved The Jones criteria were *an* attempt to overcome this difficulty in the case of rheumatic fever by placing the diagnosis on a more objective basis These criteria *originally*

From the Cardiothoracic Unit Northern General Hospital, Sheffield, England.

Received for publication July [illegible] 1975

Reprint requests Dr Christopher Ward Sheffield Cardio-Thoracic Unit, Northern General Hospital, Sheffield S5 7AU England

*Currently in receipt of British Heart Foundation Research Grant No [illegible]

Table I Jones criteria (revised) for guidance in the diagnosis of rheumatic fever (American Heart Association, 1965)

Major manifestations	*Minor manifestations*	
	Clinical	*Laboratory*
Carditis		Acute phase reactions
Polyarthritis	Previous rheumatic fever or rheumatic heart disease	Erythrocyte sedimentation rate C reactive protein leukocytosis
Chorea	Arthralgia	Prolonged P R interval
Erythema marginatum	Fever	
Subcutaneous nodules		

PLUS

Supporting evidence of preceding streptococcal infection (increased ASO or other streptococcal antibodies positive throat culture for Group A streptococcus recent scarlet fever)

"The presence of two major criteria or of one major and two minor criteria indicates a high probability of the presence of rheumatic fever if supported by evidence of a preceding streptococcal infection The absence of the latter should make the diagnosis doubtful except in situations in which rheumatic fever is first discovered after a long latent period from the antecedent infection (e g Sydenham s chorea or low grade carditis) [8]

published in 1944,[9] were modified in 1955[10] by the American Heart Association, and revised by them in 1965 [8] Table I summarizes the 1965 version of these criteria Discussion of the differential diagnosis of the various manifestations of rheumatic fever is provided in standard textbooks of rheumatic diseases and of cardiology The key to avoiding such errors is that The diagnosis of acute rheumatic fever should be made with conservatism and with insistence upon clearly expressed major clinical manifestations "[8] The consequences of failing to do this have been defined [11-14] Although these studies stress the importance of careful evaluation of physical signs, they neglect more fundamental aspects of diagnosis

Firstly, do the Jones criteria provide accurate guidelines for the diagnosis of rheumatic fever and secondly are the Jones criteria used objectively as was the original intention?

Criticism of specific aspects of the Jones criteria

There have been few published criticisms of the Jones criteria Davis[15] noted that two of the major manifestations of rheumatic fever—subcutaneous nodules and erythema marginatum—are now more frequently seen in other conditions He proposed that they should no longer be regarded as major criteria Burch and colleagues,[4] referring to the American Heart Association's revision of the Jones criteria,[8] disapproved of what they termed 'diagnosis by committee edict' Okuni[16] claimed that use of these criteria resulted in underdiagnosis of rheumatic fever This, however, was based partly on the unwarranted assumption that low grade carditis is invariably rheumatic

It is proposed here to examine four aspects of the revised Jones criteria and of the accompanying guidelines, and to show how they can be misleading particularly in the diagnosis of carditis

I Evidence of recent streptococcal infection

On the basis of earlier studies,[17-20] the authors of the revised Jones criteria were justified in claiming "The absence (of evidence of preceding streptococcal infection) makes the diagnosis doubtful [8] However the significance of evidence of streptococcal infection is not as clear cut as this comment suggests

1 Positive throat swab cultures for hemolytic streptococci can be obtained from as many as 20 per cent of asymptomatic persons in some closed communities [21]

2 It is often the case that in patients with respiratory disease from whom hemolytic streptococci are cultured, a variety of viruses can be cultured from the throat at the same time [22]

3 A rise in ASO titer occurs with some strains of hemolytic streptococcus for example groups C and G, which do not cause rheumatic fever [23] Furthermore, spuriously high levels of ASO titer are known to occur [24]

Table II Clinical and laboratory features which permit cases of viral heart disease to be diagnosed as rheumatic carditis

Different presentations of carditis as defined in the guidelines to the revised Jones criteria	*Reported incidence of different manifestations of carditis in documented viral heart disease*†				
				Koontz and Ray[15]	
	Sainani et al. 1968[8] *22 cases*	*Smith 1970*[9] *42 cases*	*Helin et al. 1968*[11] *18 cases*	*Documented Coxsackie infection 20 cases*	*No evidence of Coxsackie infection 25 cases*
Murmurs					
In an individual without previous rheumatic fever or rheumatic heart disease a significant apical systolic murmur	36		Not recorded	40	28
Cardiomegaly					
Unequivocal cardiac enlargement or an obvious increase in cardiac size in a patient with a past history of rheumatic heart disease"	64	52	44	75	76
Pericarditis					
Manifested by a friction rub pericardial effusion or definite electrocardiographic evidence	36	54	78	70	76
Congestive heart failure					
In a child or young adult in the absence of other discernible causes"	27	29	17	50	[illegible]
Minor manifestations					
Arthralgia	27		Not recorded	40	4
Leucocytosis	70	38	39	75	[illegible]
Elevated sedimentation rate	85	71	100	85	90
Pyrexia	87	69	[illegible]	85	64

Each of these categories is regarded as evidence of carditis and therefore constitutes a major manifestation of rheumatic fever (Table I)
†Figures are expressed as a percentage of the total cases in the series.

4 Following a streptococcal infection the ASO titer does not usually return to pre infection levels for 6 to 12 months[35] During this time infection with other organisms could have occurred

5 Up to 20 per cent of a normal school age population have an ASO titer in the diagnostic range[4]

Thus a raised ASO titer does not always indicate recent infection with a rheumatogenic strain[?] of streptococcus even when it does it cannot be concluded that subsequent symptoms are necessarily due to that organism The stipulation of a raised ASO titer rightly emphasizes the relationship between previous streptococcal infection and rheumatic fever but the tendency is to assume too much from its presence namely that the finding of a raised ASO titer in patients with certain clinical features is pathognomonic of rheumatic fever The fallacy of drawing such a conclusion is demonstrated by a report from Helin and colleagues[11] They observed a raised ASO titer in 3 of 16 cases of typical Coxsackie B virus myopericarditis Most of their cases would qualify for a diagnosis of rheumatic carditis on the basis of clinical findings and minor criteria (Table II) Other authors have also noted a raised ASO titer in Coxsackie virus group B infections[31]

II Exclusion of certain cases of carditis from the requirement of evidence of streptococcal infection

Evidence of preceding streptococcal infection is not required to establish the rheumatic nature of low grade carditis (see Table I) This is on the grounds that the initiating infection may have occurred weeks or months before medical advice was sought by which time the ASO titer could have returned to normal (This is arguable for as noted above[35] the ASO titer usually remains above pre infection level for 6 to 12 months) Be

that as it may, the consequences of this exclusion clause appear to have been overlooked, in these cases of isolated carditis, there is no evidence that the illness is in any way, related to previous streptococcal infection Under such conditions, there is no justification for claiming a rheumatic etiology It is relevant that Findlay[3] observed that isolated carditis was significantly less often preceded by scarlet fever than was rheumatic polyarthritis

III Diagnosis by exclusion

This is still regarded as an acceptable approach to diagnosis 'Congestive heart failure in a child or young adult in the absence of other discernible cause ' permits a diagnosis of rheumatic carditis

Viral myopericarditis is now a well recognized cause of cardiac failure (Table II) Half of Smith's cases[7] of Coxsackie virus heart disease had cardiomegaly and 29 per cent had cardiac failure, a similar incidence of cardiac failure was seen by Sainani and colleagues[8] These cases of course, would not be diagnosed as rheumatic as there was a discernible cause' (Coxsackie B virus infection) However the report of Koontz and Ray[11] highlights the danger of diagnosis by exclusion (Table II) They also studied Coxsackie B virus myopericarditis but in addition observed a group of patients, also with myopericarditis who had similar clinical and laboratory findings except for the absence of serological evidence of Coxsackie B virus infection 76 per cent had cardiomegaly and 28 per cent had a gallop rhythm It is likely that they also had viral heart disease, but because the causative agent could not be defined some of these would be accepted as cases of rheumatic carditis

IV Previous rheumatic fever or rheumatic heart disease

Patients with such a history are prone to further rheumatic attacks[ ] However its inclusion in the diagnostic criteria for rheumatic fever as a minor manifestation, virtually ensures that if they subsequently have carditis it will be diagnosed as rheumatic Cardiac enlargement an increase in cardiac size pericarditis or congestive cardiac failure (without discernible cause) come within the definition of carditis proposed in the guide lines which accompany the revised Jones criteria (Table II) A patient who presents with one of these features (each of which is common in viral heart disease) and who has a history of previous rheumatic fever or evidence of rheumatic heart disease requires only the additional presence of any one of arthralgia fever raised sedimentation rate, or leucocytosis, to qualify for a diagnosis of rheumatic carditis Each of these latter findings is common in patients with viral heart disease (Table II) In the cases described by Sainani and co workers[8] arthralgia occurred in 27 per cent, leucocytosis in 70 per cent an elevated sedimentation rate in 85 per cent and pyrexia in 82 per cent The respective figures for the series presented by Koontz and Ray[11] were 40 per cent 75 per cent 85 per cent, and 85 per cent In Smith's cases[7] leucocytosis occurred in 38 per cent, a raised sedimentation rate in 71 per cent and pyrexia in 59 per cent Thus, if viral heart disease occurs in a patient with a rheumatic history it will often fulfil the requisite criteria for diagnosis as a recurrence of rheumatic fever or carditis

These criticisms each expose the same fundamental defect in the Jones criteria, it is assumed that certain types of heart disease are invariably rheumatic This applies to cases of isolated carditis (with and without valve involvement) carditis in patients with a rheumatic history, and cases in which the etiology of the heart disease is obscure The Jones criteria are so devised that in each of these situations a diagnosis of rheumatic' can be made—even if this means waiving the requirement of supportive evidence of preceding streptococcal infection, the absence of which in other situations makes the diagnosis doubtful Thus the diagnostic approach has not changed significantly since Coombs argued that in virtually all cases of acute and chronic mitral valve disease a rheumatic etiology could be assumed because evidence of an alternative etiology was lacking Ignorance of other causes of heart disease explains this sweeping claim However, with present day understanding of the spectrum of viral heart disease Coombs rheumatic until proved otherwise approach is no longer justified

The above criticisms have indicated shortcomings which are inherent in the Jones criteria These can be partly offset by following the advice of Jones himself who was obviously aware of the dangers of using too literally the diagnostic criteria he had proposed one must constantly

search for laboratory and clinical evidence of other diseases[9] Unfortunately this is rarely done It is usual in a case of suspected rheumatic fever to end the search for an alternative etiology when a raised ASO titer is discovered (the fallacies of attaching too much importance to this investigation have been noted above) That this approach represents accepted practice is shown by the lack of any published study in which an attempt was made to detect recent virus infection in such cases—although the need for this kind of study is clearly demonstrated by the report of Helin in 1968[8] (v s) The current diagnostic criteria militate against reaching a correct etiological diagnosis in cases of isolated carditis for several reasons

1 By definition isolated carditis is not accompanied by other major manifestations diagnosis is therefore dependent on the minor criteria which are non specific

2. Evidence of recent streptococcal infection is not always demanded as supportive evidence

3 Isolated rheumatic carditis has many features in common with viral heart disease

Nowadays carditis in the absence of rheumatic polyarthritis or chorea is usually of viral origin or of undetermined etiology While the present diagnostic criteria are retained however the facility will exist to misdiagnose viral heart disease as rheumatic carditis This not only gives a false impression of the prevalence of rheumatic carditis but also hinders the elucidation of the nature of viral heart disease It would thus be more reasonable to diagnose rheumatic carditis (when other major manifestations are lacking) *only* when there is unequivocal evidence of recent streptococcal infection and when the possibility of a viral etiology has been excluded This is the reverse of the present situation

The major bar to a change in diagnostic approach is the attitude exemplified by the conclusions of Feinstein and associates[13] who analyzed cases wrongly diagnosed as rheumatic fever most diagnostic difficulties were caused either by failure to use the Jones criteria or by incorrect interpretation of them Although there was undoubtedly some justification for stating this it implies an uncritical acceptance of the infallibility of the Jones criteria and of the concept of rheumatic fever which they embody While this approach to the diagnosis of rheumatic fever persists it is unlikely that other possible etiological agents will be given serious consideration

When Jones proposed guidelines for the diagnosis of rheumatic fever in 1944[9] he emphasized that they should be used objectively and should be continuously modified Diagnostic criteria must be subject to change as knowledge increases[9] This has not happened

Summary

There are many similarities between the clinical features of viral heart disease and of rheumatic carditis as defined in the revised Jones criteria for the diagnosis of rheumatic fever Because of this it is likely that viral heart disease has been and still is diagnosed as rheumatic This situation can be avoided if isolated rheumatic carditis is diagnosed only when a viral etiology has been definitely excluded and when there is unequivocal evidence of recent infection with an appropriate strain of streptococcus

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Clinical communications

Clinical correlates of coronary cineangiography in young males with myocardial infarction

Stephen V Savran M D
A Laird Bryson M D
Thomas G Welch M D FACC
Barry L Zaret M D FACC
Ronald L McGowan M D FACC
M D Flamm Jr M D FACC
Travis AFB Calif

Before the advent of coronary angiography the presence of myocardial infarction was generally accepted as a manifestation of severe diffuse coronary artery disease More recent studies however have demonstrated that obstructive coronary artery disease in post-myocardial infarction patients can be localized to only one or two major coronary arteries The importance of this fact has been demonstrated by studies based on data from selective coronary angiography which have shown that the long term survival of patients with coronary artery disease varies inversely with the number of significantly diseased major vessels It would seem particularly important to know the extent of coronary artery disease present in young people in order to better advise them of their future activity and prognosis It would further be quite helpful if these recommendations could be made on the basis of noninvasive studies rather than coronary angiography We wish to report the results of our evaluation of 38 patients all of whom had transmural myocardial infarctions before age 40 and compare their noninvasive data with their cineangiographic findings

From th Department of Medicin Cardiology Sect on David Grant USAF Medical Center T vis AFB C lf

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Reprint requests Stephen V Sa ran Major USAF MC Department of Card logy USAF Medical Cente Scott AFB Ill 62225

Materials and methods

All patients were active duty military personnel when s udied with the exception of one recently retired 38 year old Air Force sergeant who incurred an inferior wall myocardial infarction while on active duty Prerequisites for entrance into the study were age under 40 at the time of myocardial infarction performance of selective coronary arteriography at the time of clinical evaluation and referral to our institution for reasons other than incapacitating angina pectoris congestive heart failure or recent myocardial infarction All patients were New York Heart Association functional Class I or II and were referred to our institution for evaluation of their coronary artery disease as it applied to their future military or civilian careers The patients were studied for from 2 months to 2 years after their acute transmural myocardial infarction Transmural myocardial infarction was defined as loss of R wave and/or appearance of new Q waves of at least 0 04 second in duration and 0 1 mV in depth along with clinical and enzymatic evidence of myocardial infarction All patients were evaluated by at least one staff cardiologist for historical and physical data prior to coronary angiography Blood pressures were averaged throughout the hospital stay Height and weight were recorded on all patients at the time of admission to the hospital Obesity was defined as a weight 15 per cent or more above that considered ideal by Air Force standards for a given height Chest x ray and electrocardiogram

Table I History and physical parameters

	Group I	Group II	p
Age	34 ± 2.5	35 ± 1.2	NS†
History of hypertension	3/21	1/17	NS
+FH of infarction	12/21	8/17	NS
Smokers	19/21	15/17	NS
Obesity	13/21	8/17	NS
Angina pectoris	1/21	10/17	< 0.01

+FH = Positive family history
†NS = Not significant

Table II Laboratory parameters

	Group I	Group II	p
Cholesterol (mg per 100 ml)	264 ± 52	232 ± 15	NS
Triglycerides (mg per 100 ml)	246 ± 163	156 ± 28	NS
Lipids (mg per 100 ml)	824 ± 107	741 ± 72	NS
FBS (mg per 100 ml)	97 ± 17	99 ± 7	NS
2 hr PPBS† (mg per 100 ml)	115 ± 21	116 ± 19	NS
Uric acid (mg per 100 ml)	6.8 ± 0.4	5.8 ± 0.5	< 0.001

FBS = Fasting blood sugar
†2 hr PPBS = 2 hour postprandial blood sugar

(ECG) were performed by standard methods Serum cholesterol triglycerides and total lipids were measured as previously described Fasting and 2 hour postprandial blood sugars were performed by the standard direct O toludine method on the Auto Analyzer Uric acid was also determined by the standard AutoAnalyzer method

Treadmill exercise tolerance testing was performed by the method of Bruce and Hornsten[7] to at least 90 per cent of predicted maximum heart rate in all patients with negative tests or the occurrence of angina and/or positive ST segment changes in those patients with positive tests The diagnosis of an ischemic response to exercise was made when 1 mm or greater ST segment depression horizontal or downsloping for at least 0.08 second after the J point, was noted on three consecutive beats during and/or after exercise The presence of exercise induced ventricular irritability or reproduction of chest pain was considered further confirmatory data but such tests were not considered positive in the absence of ischemic ST segment changes Selective coronary arteriography by either the Judkins or Sones technique was performed by 35 mm cineangiography at 60 frames per second with a General Electric Fluorocon II Image Intensifier System Left ventriculograms were obtained in the 30 degrees RAO-60 degrees LAO biplane positions Ventricular volumes were calculated from the single frame 30 degrees RAO left ventriculograms by the method of Sandler and Dodge[1]

Patients were divided into two groups on the basis of their cineangiographic findings Group I consisted of 21 patients Eighteen of these had a high degree (greater than 75 per cent) obstructive lesion in the major coronary artery felt to be responsible for the prior myocardial infarction but no other significant obstructive lesions Three patients with normal coronary arteriograms were placed in Group I These three patients all under age 31 at the time of their infarction had unequivocal enzyme and ECG evidence of transmural myocardial infarction and in the two patients in whom left ventriculography was able to be performed abnormal myocardial contractility in the area of the previous myocardial infarction was present Group II consisting of 17 patients had similar high degree obstructions felt to be responsible for the prior myocardial infarction as well as at least one 75 per cent or greater lesion in a major vessel anatomically removed from the area of infarction All parameters studied utilized comparison between these two groups Statistical analysis was performed with Student s t test and Fisher s test

Results

History and physical No significant differences were noted between the two groups with regard to age systolic blood pressure obesity, family history of coronary artery disease or tobacco use (Table I) Very few of the patients in Group I (3/21) or in Group II (1/17) had a history of hypertension Twelve of 21 patients in Group I and eight of 17 patients in Group II had a history of myocardial infarction in their immediate family Thirteen of the 21 patients in Group I and 10 of the 17 patients in Group II were obese The mean weights in both Groups I and II were 15 per cent above ideal Approximately 90 per cent of

both groups smoked at least one pack of cigarettes per day at the time of their myocardial infarction

In contrast to the above the presence of angina pectoris was significantly more common in Group II than in Group I Ten of the 17 patients comprising Group II had angina pectoris but only three in Group I ($p<0.01$)

Laboratory examination The two groups did not differ significantly with regard to cholesterol triglycerides fasting blood sugar 2 hour postprandial blood sugar or total lipid level (Table II) The mean uric acid of the entire study group as a whole (6.5 mg per 100 ml) did not differ significantly from that of Roth and associates [4] but the mean values between our two subgroups did differ significantly ($p<0.001$) No patient in either group had clinical gout and no serum uric acid was greater than 8.2 mg per 100 ml

Noninvasive studies Chest posterior anterior and lateral x ray examinations were similar in both groups with no evidence of left ventricular enlargement or left ventricular aneurysm noted There was no significant ECG difference between the two groups with regard to resting ischemic ST segment changes presence of left ventricular hypertrophy or infarct localization (Table III) Eleven patients in Group I had anterior wall myocardial infarction eight had inferior wall myocardial infarction and two had a lateral wall myocardial infarction In Group II seven patients had an anterior wall infarction eight had inferior wall myocardial infarction and two had nonspecific ST segment changes only

In contrast to the resting ECG the difference between the two groups in response to the maximal exercise tolerance test was statistically highly significant ($p < 0.001$) (Table IV) A total of 29 patients underwent exercise testing Seventeen of 21 patients in Group I were tested 13 did not manifest ischemic ST segment changes at any time during the test whereas one patient developed 1 mm ST segment depression at 6 minutes after exercise that had resolved by 9 minutes after exercise and was not associated with pain Three studies were equivocal due to resting ST segment abnormalities angina was not present in these three patients The three patients with angina in Group I all had negative maximal exercise studies The three patients with normal coronary arteriograms all had normal exercise tolerance and none had angina Twelve of 17 patients in Group II were exercised and all demonstrated ischemic ST segment changes Of these 12 patients five had no prior history of angina pectoris and did not have chest pain during the exercise test One patient in Group I had a run of three consecutive premature ventricular contractions during recovery and two patients in Group II had at least a 10 beat run of ventricular tachycardia during the exercise phase of the test that reverted spontaneously No other complications of exercise testing were noted in either group

Coronary angiography (Table V) Thirty five patients had at least 75 per cent obstruction of at least one coronary artery Of these nine patients had a significant lesion of only the left anterior descending and nine had a significant lesion of only the right coronary artery Eight patients had significant two vessel disease (six left anterior descending plus right coronary artery one left anterior descending plus left posterior circumflex

Table III ECG findings

	Group I (%)	*Group II* (%)
Anterior MI	52	41
Inferior MI	38	47
Lateral MI	10	0
ST T wave changes	0	12

MI = Myocardial infarction

Table IV Treadmill results

	Group I	*Group II*
Positive	1	12
Negative	13	0
Equivocal	3	0

$p < 0.001$

Table V Obstructive coronary artery lesions

	Group I	*Group II*
None	3	
One vessel		
LAD	9	
RCA†	9	
Two-vessel		8
Three vessel		9

LAD = Left anterior descending coronary artery
†RCA = Right coronary artery

one right coronary artery plus left posterior circumflex), and nine had significant three vessel disease. Three patients, as discussed previously, had normal coronary arteries. All Group I patients therefore had single vessel obstructive disease equally distributed to the left anterior descending and right coronary artery, or normal coronary arteries; all Group II patients had at least two vessel obstructive disease. No significant differences were noted on the left ventriculograms between the two groups with regard to ejection fraction. Two out of 21 patients in Group I and three out of 17 patients in Group II had normal left ventriculograms while the remainder of the patients had abnormal segmental contractility in the area of the previous myocardial infarction.

Discussion

This patient group as a whole is similar to previously reported group studies of young males with coronary artery disease with respect to age, obesity, cholesterol, triglycerides, total lipids, uric acid, blood sugar, family history, and smoking history.[1-11] There were no differences between Groups I and II in any of the epidemiologic factors studied except for the serum uric acid level. These epidemiologic data suggest that although the application of atherosclerotic risk factors can be used as a predictive tool in large population studies to determine those individuals at increased risk for developing coronary artery disease,[12] these same risk factors do not separate the groups of young post-myocardial infarction patients with localized single vessel disease from those with multivessel involvement.

The presence of angina pectoris was significantly more common in Group II than Group I ($p < 0.001$), but overlap was seen. Fourteen per cent of Group I patients were felt to have typical angina pectoris whereas 44 per cent of patients in Group II with significant additional obstructive disease were symptom free and had no pain during their exercise studies. This overlap is not surprising as severe atherosclerosis can often be present in asymptomatic individuals but does diminish the value of this symptom alone in distinguishing between these two groups. The treadmill exercise tolerance test performed by the Bruce protocol was an effective means of discriminating those patients with additional obstructive disease from those without. We found it quite interesting that, whereas the seven Group II patients with clinical angina had reproduction of their pain during the treadmill, none of the five patients in this group without angina had chest pain while testing. In this group of patients, therefore, the exercise ECG was much more sensitive than the clinical history of angina.

The almost uniform lack of ischemic ST segment changes during exercise testing in Group I patients deserves comment. We feel that these patients do not, in fact, develop myocardial ischemia during maximal exercise testing as their coronary artery disease is localized only to a vessel supplying infarcted myocardium. Their functional response to the maximal exercise tolerance test, therefore, appears similar to that of normal subjects, not to that of patients with single vessel obstructive disease without myocardial infarction.

Fifty one per cent of our patients had only single vessel obstructive disease. This figure is considerably higher than those reported in groups not similarly age restricted. Proudfit and associates[4] found a 10.5 per cent incidence of isolated right coronary artery lesions and a 22.4 per cent incidence of isolated left anterior descending lesions; Gensini and Kelley found 9 and 33 per cent incidence, respectively. The higher incidence of single vessel obstructive disease in this younger population may explain Roth's observation that young men with acute myocardial infarction have fewer acute complications and less long term disability than their older counterparts.[11] Our group of patients have not been followed longitudinally so that progression of their coronary artery disease is not yet known. Presumably they would be expected to follow the trend of less age restricted groups of patients and demonstrate a more or less linear yearly mortality rate related to the number of major coronary arteries obstructed.[4,5] It would be interesting to speculate, however, whether the life span of our patients with myocardial infarction and isolated single vessel disease will in fact follow the mortality curve of those patients with single vessel disease without infarction or if, having survived an infarction in the distribution of their only significant coronary lesion with no objective evidence of residual ischemia, these patients will have a more nearly normal life expectancy.

In conclusion, the absence of angina pectoris and the presence of a negative submaximal exer

cise test in young males who have a history of transmural myocardial infarction can be considered strong evidence against the presence of additional obstructive coronary artery disease and may obviate the need for coronary cineangiographic study in this group of patients The question of whether this will have prognostic value in these young post-myocardial infarction patients will be answered only by longitudinal studies

Summary

Thirty-eight men who suffered acute transmural myocardial infarction before age 40 and after recovery were New York Heart Association functional Class I or II were studied by noninvasive means and by coronary angiography in order to determine whether these noninvasive studies could predict the presence of significant coronary artery disease remote from that felt to be responsible for the previous myocardial infarction Patients were divided into two groups on the basis of the absence (Group I) or presence (Group II) of obstructive disease in a major coronary artery supplying myocardium remote from the prior myocardial infarction There were 21 patients in Group I and 17 patients in Group II They did not differ with respect to age abnormalities of lipid or glucose metabolism family history history of hypertension or cigarette use presence of obesity or infarct localization Ten of 17 patients in Group II had angina pectoris only 3/21 patients in Group I had angina pectoris ($p < 0.01$) All 12 patients tested in Group II had a positive maximal exercise tolerance test only 1/17 patients tested in Group I was similarly positive ($p < 0.001$) The absence of angina pectoris and the presence of a negative maximal exercise tolerance test is strong evidence against the pressure of significant CAD remote from that responsible for the prior myocardial infarction

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A combined electrophysiological and anatomical study of the human fetal heart

Michiel J Janse
Robert H Anderson
Frans J L van Capelle
Dirk Durrer
Amsterdam The Netherlands

Most electrophysiological investigations of cardiac tissues have been performed in animal species other than man Although these studies have provided considerable information regarding the electrical activities of the heart the question always remains as to whether the conclusions reached are valid with regard to the human subject From the limited data obtained from isolated human hearts[1,2] it would seem that comparison in a broad context with animal results is valid and permissible The results of Tuganowski and Cekánski[3] suggested however that human fetal hearts were functionally mature from an early age a fact at variance with data obtained from young animals by Preston, McFadden and Moe[4]

This is of some significance, since the results of these animal experiments have been interpreted as constituting a possible factor in the production of the sudden death in infancy syndrome[5] We have recently had the opportunity to study a limited number of fetal hearts using both anatomical and electrophysiological techniques to the best of our knowledge a correlation not previously attempted in the isolated human heart

Our correlative findings in two preparations were particularly referable to the problem of functional maturity of the conducting tissues Our findings were also significant to the vexatious topic of 'specialized internodal pathways'[6-10] They were also pertinent to the related topic of atrial 'plateau' fibers[11] For these various reasons our findings are presently described

Materials and methods

Five fetuses of crown rump length 100 (2) 125 136 and 165 mm were available for study Their gestational ages varied between 12 and 16 weeks They were obtained at lower segment section for therapeutic abortion In the first two experiments the ventricles were removed for investigations in another department Only a small piece of interventricular septum remained These preparations demonstrated complete atrioventricular block

In the latter three experiments electrocardiograms were obtained immediately on delivery These revealed sinus rhythm and 1 1 atrioventricular conduction at a PR interval varying between 85 and 100 msec In all cases the hearts were rapidly removed and placed in oxygenated Tyrode solution The right side was opened by a lateral incision in the tricuspid orifice and the septal surface exposed, taking care not to damage any of the muscle bands of the atrial septum The experimental and recording procedures were as routinely performed for animal studies in our laboratory and have been described elsewhere[12] Recordings were made with both glass microelectrodes and multiple linear surface electrodes After completion of recordings the entire preparation was processed for histology Three specimens were prepared for sectioning in a cryostat and

From the Department of Cardiology and Clinical Physiology Wilhelmina Gasthuis University of Amsterdam and The Interuniversity Cardiological Institute The Netherlands

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Reprint request Dr M J Janse Department of Cardiology and Clinical Physiology Wilhelmina Gasthuis Eerste Helmerstraat 101 Amsterdam The Netherlands

R H Anderson was a MRC Travelling Fellow United Kingdom Present address Cardiothoracic Institute Brompton Hospital Fulham Rd London England

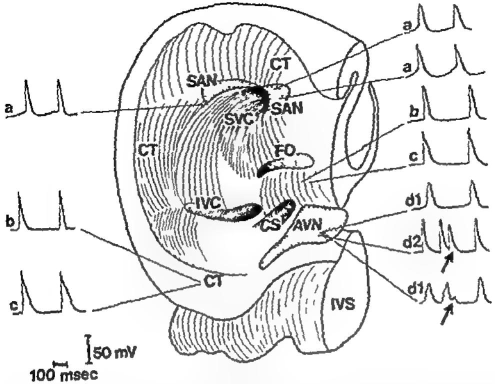


Fig 1 Drawing of a reconstruction of the right atrium of a 165 mm human fetus The septal musculature is divided into bands by the venous ostia superior vena cava (*SVC*) inferior vena cava (*IVC*) coronary sinus (*CS*) and the foramen ovale (*FO*) The crista terminalis (*CT*) is a broad muscle bundle forming the junction between primitive atrium and primitive sinus venosus and extends downward toward the interventricular septum (*IVS*) medial and lateral columns The sinuatrial node (*SAN*) is located at the junction of the *SVC* with the crista but is superior to the crista so that only its junctional zones are visible in the reconstruction The atrioventricular node (*AVN*) is a large structure located between the *CS* and the central fibrous body the latter not being shown on the reconstruction. The action potentials were recorded from cells impaled at the position of the marking lines Cells marked *a* showing diastolic depolarization were recorded from the junctional areas of the *SAN* with the *CT* Action potentials within the atrium could be divided into those exhibiting plateau (*type c*) and those without this plateau (type b) The cells were often adjacent as demonstrated and moments of excitation of such adjacent cells were identical Action potentials marked *d* were recorded only from the region of the compact atrioventricular node Trace *d2* and the lower trace of *d1* were recorded simultaneously during stimulation of the atrium demonstrating conduction block of an induced atrial premature beat (arrowed) The upper trace of *d1* was recorded during spontaneous rhythm

sections produced were processed for both histology and cholinesterase activity The other specimens were routinely prepared by embedment in paraffin wax All sections were cut in the frontal plane of the heart at 10 to 20 micron thickness The first specimen studied was subsequently reconstructed by drawing each third section onto 1 cm thick material with a magnification factor of 33 times The outline was then cut round and the sections reassembled The reconstruction is illustrated in Fig 1

Results

1 Microelectric recordings Action potentials comparable to those obtained in rabbit hearts were obtained In the atrium both specialized and nonspecialized cells were impaled The specialized cells were confined to the cardiac nodes The sinuatrial node was difficult to localize and subsequent sectioning of the tissues and reconstructions revealed that the node was inaccessible by our method of tissue preparation (Fig 1) Only a few cells exhibiting diastolic depolarization were impaled but all came from the region of junction of the sinuatrial node with the medial and lateral columns of the crista terminalis (Fig 1) Cells exhibiting action potentials typical of the atrioventricular node were recorded from the area between the coronary sinus and the central fibrous body Cells showing

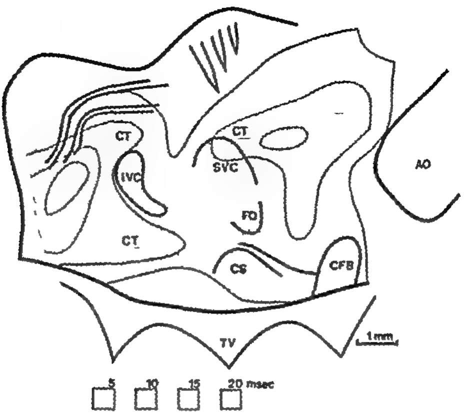


Fig 2 Map of the endocardial surface of the right atrium of a 125 mm human fetus The activation sequence was determined with surface electrodes The isochrones indicate two areas of early endocardial breakthrough shown by subsequent histology to correspond with the junction of the sinuatrial node with the lateral and medial columns of the crista terminalis The broad wave fronts form a dual input to the atrioventricular junctional area between the coronary sinus and the central fibrous body—*CFB* Other abbreviations as for Fig 1 together with *AO*=aorta and *TV*=tricuspid valve

notched action potentials were recorded from only a limited area subsequently shown to be consistent with the compact zone of the node (Fig 1) The atrial cells between the nodes exhibited two types of action potential one of plateau type and the other of nonplateau type The plateau potentials were recorded in great frequency in the superior atrium but also extended toward the fibrous anulus They were intermixed with cells exhibiting action potential without a plateau There was no difference between moments of activation of the two types No correlation was obtained between occurrence of plateau fibers and histological or morphological characteristics (Fig 1)

2 Atrial mapping In three preparations atrial activation was mapped In all these preparations, activation proceeded through the atrial septum and crista terminalis as broad wave fronts (Fig 2)

In two experiments two distinct broad fronts extended from the medial and lateral columns of the crista toward the atrioventricular nodal region providing a dual nodal input (Fig 2)

In the other experiment, activity spread broadly down the anterior part of the septum with later activation of the lateral column of the crista The sites of early activity correlated with the junction of sinuatrial node with the crista

Narrow zones of activity propagating in advance of neighboring activity were not identified Histology of the atrial tissues in all cases showed that only the sinuatrial and atrioventricular nodes exhibited features of specialized tissue The remaining myocardium was homogenous, being divided into muscle bands by the holes in the septum The results with the cholinesterase technique confirmed the absence of any internodal tracts of specialized tissue

3 Stimulation studies Refractory periods of the atrial and ventricular myocardium were measured in one heart The functional refractory periods of the A V conducting system were ascertained by applying premature test stimuli to both the atrium and the ventricle during regular stimulation Recordings were made from the atrium and from the right bundle branch (RBB) at a site halfway between the fibrous anulus and

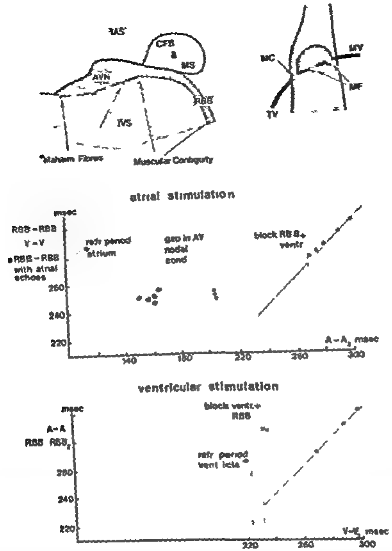
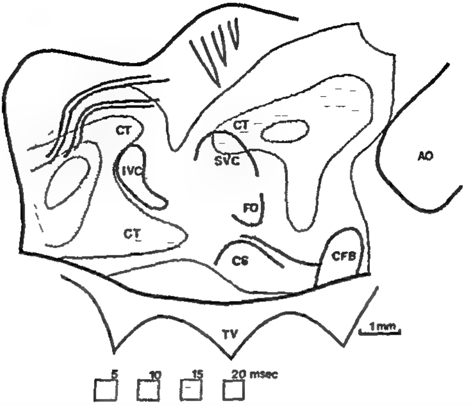


Fig 3 Data relative to the heart from a 100 mm human fetus (approx 12 weeks gestational age) The top panel demonstrates the results of histological sectioning The fibrous anulus was poorly formed, so that the atrioventricular node (*AVN*) was contiguous throughout its length with the ventricular septum (*IVS*) Similarly the common bundle and right bundle branch (*RBB*) were in histological contiguity with ventricular myocardium The nodal connections were comparable with Mahaim fibers (*MF*) There was additional muscular contiguity between atrial overlay fibers and the ventricular septum (upper right panel—*MC*) The right panel represents a cross-section through the nodal region *IAS* interatrial septum *MS* membranous septum *CFB* central fibrous body *MV* mitral valve *TV* tricuspid valve The middle panel demonstrates results of stimulation of the right atrium close to the sinus node at the basic rate of 3.0 msec and the lower panels show results of stimulation of the right ventricle at the same basic rate After every tenth basic beat, a test stimulus was given at progressively shorter intervals indicated on the abscissae of both graphs The ordinate of both graphs represents in the middle panel the corresponding intervals between (1) the complexes of the right bundle branch recorded during the last basic beat and from the premature beat (*RBB*–*RBB*) and (2) the complexes of ventricular myocardium recorded from the basic and premature beats (V–V) Similarly the intervals *A*–*A* and *RBB*–*RBB* shown in the lower panel indicate intervals between basic beat and premature beat during retrograde studies. It will be seen that during atrial stimulation (middle panel) premature beats with an interval between 170 and 200 msec are not conducted through the AV node At shorter intervals premature beats are conducted but are always accompanied by atrial echo beats. It can also be seen that the specific conducting system protects the ventricle from being excited by supraventricular impulses in its vulnerable period The vulnerable period coincides with the ventricular refractory period which is 225 msec (lower panel) Conduction block between RBB and ventricle occurs at an A–A interval of [illegible]0 msec the shortest interval between two conducted ventricular impulses (V–V) is 290 msec



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Similar findings of mature conducting tissues in neonates were recently reported in brief by Bekheit and associates.[20] Our anatomical findings are of further interest since they demonstrate that the functional maturity in the fetus is produced despite a marked morphological immaturity of the conducting system.

In the specimens we studied, the node and bundle were contiguous throughout their length with ventricular myocardium, the fibrous anulus being incompletely formed. Such connection through gaps in the anulus are comparable to the fibers described by Mahaim.[15] Notwithstanding this anatomic contiguity, the conduction pathways were functionally isolated from the ventricular myocardium. This finding suggests that the mere demonstration of nodo-ventricular communications in the human heart is not proof of their function as an accessory conduction pathway. Nonetheless, a recent study by Lev and associates has shown that in some circumstances connections of the "Mahaim" variety can function as a pathway for pre-excitation. These results indicate that further study is necessary to elucidate the role of these connections.

Our mapping experiments demonstrated that atrial activation occurred as broad fronts along the prominent atrial muscle bundles. Any division of these fronts was dependent upon the architecture of the septum. Such results are in keeping with previous studies in the human heart by Durrer and associates and Brusca and Rosettani and with the findings of Spach and associates and ourselves in animal hearts. Our present studies further demonstrate that in histological terms the atrial septum is composed of homogeneous myocardium of the "working" variety and that histologically specialized tracts could not be identified. We were also unable to distinguish any histochemically distinct tracts within the septum, unlike Truex, who reported such tracts in the ferret heart. We have concluded on the basis of our present combined electrophysiological, histological, and histochemical studies that internodal conduction occurs through plain atrial myocardium. Our investigation therefore denies the existence of so-called "specialized internodal pathways" as described by James.[8] Recent review of the literature has also cast doubt on the concept of specialized internodal conduction.

Finally, our results are of interest with regard to the occurrence of "plateau" fibers. Recording of such potentials has been considered by Hogan and Davis[11] as a possible index of the specialization of an atrial fiber. Such fibers in the human fetal heart have presently been found dispersed throughout the atrium, an observation previously noted by both Gennser and Nillson[3] and Tuganowski and Cekánski. Furthermore, we were unable to note any correlation between plateau fibers and morphological and histological features, while the fibers exhibiting these potentials were not activated in advance of neighboring nonplateau fibers. The significance of the fibers to atrial activation is therefore unsure. The solution as to whether these fibers are either functioanlly or morphologically distinct from nonplateau fibers will be provided only by the performance of combined anatomical-electrophysiological experiments which use cellular marking techniques at the level of the electron microscope.

Summary

Five human fetal hearts of gestational ages ranging from 12 to 16 weeks were studied with both electrophysiological and anatomical techniques. The electrophysiological behavior of these hearts was comparable with results obtained with other animal species and adult human hearts. This indicates that the fetal heart is *functionally* mature from an early stage of development, however, the tissues are not fully differentiated from an anatomical standpoint.

Results of mapping experiments indicated that atrial activation occurred through broad wave fronts and no electrophysiological evidence was found to support the concept of "specialized internodal conduction." In two hearts, the node and bundle were *found* to be in anatomical contiguity with ventricular myocardium throughout their length, but the conducting tissues *were* already *functionally* insulated from the ventricles.

The results have significance with regard to concepts of the "sudden death in infancy syndrome" and ventricular pre-excitation.

The authors are grateful to Professor G. J. Kloosterman, Dr. J. J. der Weduwen, and Dr. P. E. Treffers, Department of Obstetrics and Gynaecology, University of Amsterdam, for their enthusiastic cooperation. Thanks are due to Mrs. Carla Mater for expert technical assistance and to Dr. G. E. Freud for his assistance in one of the experiments.

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septal papillary muscle During atrial stimulation, conduction block occurred first at the junction of right bundle branch with ventricular myocardium at an A1 A2 interval of 268 msec With increasing prematurity of A2 conduction time through the A V node increased until complete block occurred at an A1 A2 interval of 200 msec The precise site of block is unknown, it could have occurred within the AV node but possibly also in the His bundle Further shortening of the A1 A2 interval demonstrated the presence of the gap phenomenon, ' conduction to the right bundle branch occurring again at A1 A2 intervals ranging from 160 to 168 msec All these conducted beats were associated with atrial echoes (See Fig 3) A2 RBB2 conduction time at these very short A1 A2 intervals varied from 190 to 200 msec whereas A2 echo intervals varied from 208 to 240 msec

During ventricular stimulation block occurred at the junction of ventricular myocardium with the right bundle branch at a V1 V2 interval of 232 msec It appeared that conduction in the direction of muscle conducting tissue was easier than conduction in the opposite direction since during atrial stimulation block at the junction occurred at an A1 A2 interval of 268 msec The refractory periods of atrial and ventricular myocardium were 115 and 225 msec respectively

It is important to stress the fact that during atrial stimulation the shortest interval between two conducted impulses at the level of the ventricular myocardium was 282 msec that is 57 msec longer than the refractory period of the ventricular myocardium Thus the specific conducting system protected the ventricle from being excited by supraventricular impulses in its vulnerable period the latter occurring at the end of the refractory period Even at the level of the right bundle branch the shortest interval between two conducted beats was 235 msec 10 msec longer than the ventricular refractory period During both atrial and ventricular stimulation the impulses were conducted only via the specialized conducting system Although functionally mature, when studied with histological criteria the heart was found to be immature The node and right bundle branch were in muscular contiguity with ventricular myocardium throughout their length since both the anulus fibrosus and the fibrous tissue sheath of the A V bundle were incompletely formed (Fig 3) Atrial overlay cells were also in direct contiguity with ventricular myocardium Despite the histological contiguity, the conducting system functioned as though isolated from the ventricle Pre excitation was not present, the PR interval recorded immediately on delivery of the fetus being 0 85 sec neither could pre excitation be provoked by premature stimulation In one other heart derived from a fetus having the same gestational age and crown rump length (circa 12 weeks and 100 mm, respectively) test stimuli were also applied A complete set of curves could not be made because 2 1 A V block developed during the course of the experiment, presumably due to mechanical stress of the preparation during mounting in the tissue bath It could be established that the conducting system was functionally isolated from the ventricles and that pre excitation did not exist, and could not be provoked Nonetheless, as in the heart described above histological contiguity was observed between the length of the A V junctional area and the crest of the ventricular septum

Discussion

In general terms our findings are in agreement with those of previous studies on isolated human fetal hearts which used microelectrodes[1 4] and surface and intramural electrodes[5] We believe however that several specific findings are of clinical importance Our recordings and stimulation findings show that the conducting tissues in the human fetal heart at 12 weeks gestation function in a manner comparable to that observed in the adult heart

This functional maturity was previously noted by Tuganowski and Cekánski[4] following their microelectrode studies It is in marked contrast to results obtained in young goats pigs and sheep[6] These demonstrated important differences in the refractory periods of the different cardiac tissues when compared with those obtained in adult animals As a result it was possible for premature atrial beats to reach the ventricular myocardium in its vulnerable period and hence initiate ventricular fibrillation On the basis of these findings, it was suggested by Dawes[7] that similar sequences in the young human heart may be a factor in the production of sudden death in infancy Our observations contend against this possibility and show that, at least in the isolated human fetal heart the atrioventricular conduction system would protect the ventricles in the same manner as does this system in the adult

Similar findings of mature conducting tissues in neonates were recently reported in brief by Bekheit and associates[14] Our anatomical findings are of further interest since they demonstrate that the functional maturity in the fetus is produced despite a marked morphological immaturity of the conducting system

In the specimens we studied the node and bundle were contiguous throughout their length with ventricular myocardium the fibrous anulus being incompletely formed Such connection through gaps in the anulus are comparable to the fibers described by Mahaim [3] Notwithstanding this anatomic contiguity the conduction pathways were functionally isolated from the ventricular myocardium This finding suggests that the mere demonstration of nodo ventricular communications in the human heart is not proof of their function as an accessory conduction pathway Nonetheless a recent study by Lev and associates has shown that in some circumstances connections of the Mahaim variety can function as a pathway for pre excitation These results indicate that further study is necessary to elucidate the role of these connections

Our mapping experiments demonstrated that atrial activation occurred as broad fronts along the prominent atrial muscle bundles Any division of these fronts was dependent upon the architecture of the septum Such results are in keeping with previous studies in the human heart by Durrer and associates and Brusca and Rosettani and with the findings of Spach and associates[1] and ourselves[6] in animal hearts Our present studies further demonstrate that in histological terms the atrial septum is composed of homogeneous myocardium of the working variety and that histologically specialized tracts could not be identified We were also unable to distinguish any histochemically distinct tracts within the septum unlike Truex [8] who reported such tracts in the ferret heart We have concluded on the basis of our present combined electrophysiological histological and histochemical studies that internodal conduction occurs through plain atrial myocardium Our investigation therefore denies the existence of so called specialized internodal pathways as described by James Recent review of the literature has also cast doubt on the concept of specialized internodal conduction

Finally our results are of interest with regard to the occurrence of plateau fibers Recording of such potentials has been considered by Hogan and Davis[11] as a possible index of the specialization of an atrial fiber Such fibers in the human fetal heart have presently been found dispersed throughout the atrium an observation previously noted by both Gennser and Nilsson[3] and Tuganowski and Cekánski[4] Furthermore we were unable to note any correlation between plateau fibers and morphological and histological features while the fibers exhibiting these potentials were not activated in advance of neighboring nonplateau fibers The significance of the fibers to atrial activation is therefore unsure The solution as to whether these fibers are either functioanlly or morphologically distinct from nonplateau fibers will be provided only by the performance of combined anatomical-electrophysiological experiments which use cellular marking techniques at the level of the electron microscope

Summary

Five human fetal hearts of gestational ages ranging from 12 to 16 weeks were studied with both electrophysiological and anatomical techniques The electrophysiological behavior of these hearts was comparable with results obtained with other animal species and adult human hearts This indicates that the fetal heart is functionally mature from an early stage of development however the tissues are not fully differentiated from an anatomical standpoint

Results of mapping experiments indicated that atrial activation occurred through broad wave fronts and no electrophysiological evidence was found to support the concept of specialized internodal conduction In two hearts the node and bundle were found to be in anatomical contiguity with ventricular myocardium throughout their length but the conducting tissues were already functionally insulated from the ventricles

The results have significance with regard to concepts of the sudden death in infancy syndrome and ventricular pre excitation

The authors are grateful to Professor G J Kloosterman Dr J J der Weduwen and Dr P F Treffers, Department of Obstetrics and Gynaecology University of Amsterdam for their enthusiastic cooperation Thanks are due to Mrs Carla Mater for expert technical assistance and to Dr G E Freud for his assistance in one of the experiments

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Incidence of intermembrane alterations in human heart mitochondria A preliminary ultrastructural study

Marilyn N Smith M A
Marcella Klima M D
Houston Texas

The ultrastructure of heart mitochondria has been investigated from many aspects Under conditions of ischemia mitochondria show characteristic changes consisting of swelling cristae disruption and formation of large matrix granules [1] Similar mitochondria changes are seen during autolysis

The intermembrane space of mitochondria was for many years thought to be filled with merely a watery fluid devoid of any structural features Intermembrane paracrystalline arrays of a complex nature were reported in skeletal muscles from cases with myopathic disturbances In 1968 Newcomb and associates reported a membrane junction like structure in bean root mitochondria which consists of apparently fused outer layers of two unit membranes forming a broad flat plate like crista Several recent reports of an intermembrane structure somewhat resembling a tight junction in animal heart mitochondria[7] and in animal skeletal muscle mitochondria[11] have brought the intermembrane space into prominence

Burch Cheah [1] and Saito and their co workers have shown a relationship between the occurrence of these structures and autolytic changes related to storage of tissue after the death of an animal Herdson and associates[3] in the fine structure study of autolytic changes in dog myocardium did not however report their presence in tissue removed from the animal for up to 3 hours Several studies on isolated heart mitochondria also fail to mention the presence of these structures [1] Mitochondria from human hearts stored for up to 7 days in a portable preservation chamber did not exhibit this structure [7] It is interesting to note that intermembrane structures were not reported in ultrastructural studies in experimental hypertrophy by McCallister and Brown [14]

We first became aware of this mitochondrial membrane change in the study of three cases of stone hearts In open heart surgery 0 3 per cent of the patients develope a spastic contraction of the left ventricular myocardium which cannot be relaxed either by chemical or physical means [19] The ventricular muscle is as hard as stone" to palpation and has been named the stone heart syndrome [21] One sample was collected as a surgical biopsy and thus the mitochondrial deposits could not represent postmortem changes These mitochondrial alterations have not been reported previously in human heart tissues and their presence in surgical biopsies must be dealt with and recognized either as an autolytic change occurring in damaged cells or as an unknown biochemical alteration expressed as a morphologic alteration to attempt to overcome an adverse environment in the heart muscle We examined other heart specimens both surgical and autopsy to attempt to correlate these specific mitochondrial alterations with pathologic conditions

Material and methods

Twenty human hearts as in Tables I and II were examined by electron microscopy The sample was taken from the wall of the left

From the Department of Pathology St Luke's Episcopal Hospital Veterans Administration Hospital and Baylor College of Medicine Houston Texas

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Reprint requests Marcella Klima M D Department of Pathology Veterans Administration Hospital Houston Texas 77031

Table I Comparison of ultrastructural features observed in myocardial samples obtained at surgical biopsy

				Ischemic changes					Intermembrane alterations		
						Mitochondria					
Case	Surgical situation	Sex	Age (yr)	Margination of chromatin	Glycogen	Swelling	Cristae disrupt	Matrix granules	Rim	Cristae	Hypertrophy
1	Aortic valve replacement	F	48	+	++++	–	–	–	–	–	
2	Coronary artery bypass	M	60	+	++++	–	–	–	–	–	–
3	Biopsy	M	49	++	++++	+†	+†	–	–	–	++
4	Left ventricular aneurysm resection	M	52		++++	++	+	–	–	+	
5	Right atrial appendage	M	40	++++	+++	++++	++++	++++	+	+	++
6	Aortic valve replacement	F	25		++	+++	++	–	–	–	
7	Left ventricular aneurysm resection	F	62		+	+‡	+	–	–	–	
8	Idiopathic myocardiopathy biopsy	M	19	++	+	+	+	–	+	+	+++
9	Biopsy	F	51	+++	+	++++	++++	–	–	–	++
10	Stone heart	F	56	+	+§	++	++	–	++	–	

Negative (–) indicates the absence of a characteristic Positive (+) indicates the presence of characteristics Characteristics were subjectively rated on a + to ++++ scale (since mitochondrial plates were never seen in more than 50 per cent of the mitochondria in a section four plus indicates their presence in 50 per cent of the mitochondria) Blank spaces indicate no information available

†Slight

‡Localized

§Sparse

ventricle except where another site is indicated Tissue was fixed in 3 per cent glutaraldehyde in phosphate buffer pH 7 4 After a buffer rinse fixation was continued with 1 per cent OsO_4 in phosphate buffer The specimen was divided and half was treated with 1 per cent aqueous uranyl acetate for 1 hour before standard dehydration The specimen examined was usually the one without en bloc treatment with uranyl acetate so that glycogen could be visualized Tissues were embedded in a mixture of Epon and Araldite resin, blocks were sectioned with an LKB Huxley microtone and sections were poststained with alcoholic uranyl acetate followed by lead citrate Sections were examined with a Siemens 101 microscope

Evaluation of myocardial changes was made on a subjective basis with no attempt at a statistical analysis Also samples are from a single area of each heart and thus do not reflect possible variation from one site to another

Results

The findings of the incidence of ischemia or autolytic changes and of the occurrence of intermembrane alterations in mitochondria are summarized in Tables I and II The amount of glycogen remaining in the muscle was used as a guide to indicate the amount of ischemia but glycogen depletion does not entirely correlate with other indications of ischemia such as, margination of chromatin and mitochondrial changes (swelling cristae disruption and matrix granule formation) In four out of the 10 surgical biopsies examined intermembrane changes were found There appears to be no correlation between their presence and the amount of glycogen or other ischemic changes

The ten specimens obtained at autopsy were compared according to times after death of tissue fixation Small amounts of glycogen remained in only four of the 10 specimens Other autolytic changes swelling of mitochondria cristae disruption, and matrix granule formation were present to some degree in all specimens Intermembrane alteration of mitochondria occured in nine of 10 specimens but there was no clear correlation between their frequency and time after death that tissue was obtained Alterations in cristae were more frequent than changes in the outer

Table II Comparison of ultrastructural features observed in myocardial samples obtained at autopsy at various times after death*

							Ischemic or autolytic changes					Intermembrane alterations	
									Mitochondria				
Case	Cause of death	Sex	Age (yr)	Time after death of tissue fixation (hr)	Heart weight (Gm)	Anatomic description of hypertrophy	Margination of chromatin	Glycogen	Swelling	Cristae disrupt	Matrix granules	Rim	Cristae
1A	Congestive heart failure	M	[illegible]	1	610	Minimal	++++	−	++	+++	+	+	+
2A	Thrombocytopenic purpura	F	20	1 1/"	430	Mild bilateral more at left	++++	−	++++	++++	+	−	++++
3A	Stone heart syndrome	M	50	*	7?0	Concentric left severe	+	+	++	+++	++	+	++
4A	Arteriosclerosis	M	[illegible]	2 1/2	300	None	+++	+	+	+	++	−†	−†
5A	Alcoholic cardiomyopathy	F	?2	6	300	Left ventricular moderate	++	−	+++	+++	++++	+	++++
6A	Ruptured aortic aneurysm	M	56	6	390	Left ventricular concentric marked	++++	+	+++	++	+++	++	++++
7A	Cardiac failure in aortic stenosis	M	71	6	450	Left ventricular	+++	−	+++	++	+	+	++
8A	Rheumatic heart disease	M	20	6	960	Marked	++	−	++	++	+	−	+
9A	Stone heart syndrome			Unknown	Unknown	Unknown	++++	−	++	+++	++++	++	++++
10A	Lymphoepithelioma	F	47	12	180	None	+++	+	++	+++	++++	++	++++

*See footnote on Table I

†Specimen was tho ghly searched

rim Heart weight was compared to determine if there appeared to be a correlation with hypertrophy None was found

Intermembrane alterations occur both in the cristae and in the outer rim of mitochondria In some sections they appeared as a dense deposit between the two membranes (Fig 6) The inner and outer membranes were slightly pushed apart by the interposed material Some evidence of periodicity of the intermembrane material was seen (Fig 7) In many sections a distinct center layer could be seen (Figs 3 and 5) The total width of the five layered alteration is 220 to 240 A The three dense layers are about 60 A and the two intervening spaces about 30 A wide The two outer layers are clearly part of the trilamellar mitochondrial membrane system (Figs 6 and 7) but the inner dense layer has not been observed with a distinct trilamellar configuration and may in fact, be slightly narrower than the unit membranes

At low magnification the altered mitochondria could be spotted because they often have one flat side (Fig 1 double arrow) Mitochondria with the membrane alteration in the cristae were observed in fields that have alterations in the rim but the two kinds have never been observed together in a single mitochondrion Since the intermembrane space in the rim is continuous with the intermembrane space in the cristae one might expect the

Fig 1 Heart sample taken 6 hours after death from a patient who died of alcoholic cardiomyopathy (Case 5A) At least 50 per cent of the mitochondria have membrane alterations both in the rim (double arrow) and in cristae (single arrow) Characteristic autolytic changes are present clumping of chromatin glycogen depletion mitochondrial swelling cristae disruption and granule formation Numerous lipofuscin granules are in the perinuclear region (×12 000)

Fig 2 Surgical biopsy specimen from a patient operated upon for left ventricular aneurysm (Case 7) Note the altered cristae There is some mitochondrial swelling and cristae disruption but ischemic changes are mild (×20 000)

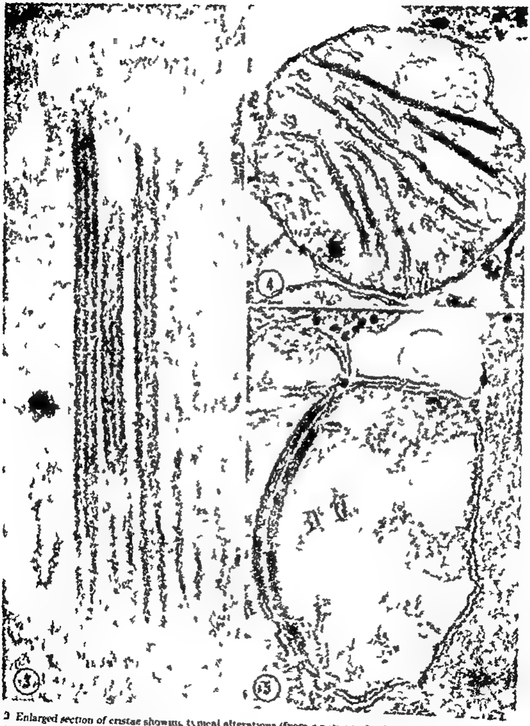

Fig 3 Enlarged section of cristae showing typical alterations (from a patient who died of cancer Case 10A) The heart was small with no evidence of hypertrophy (×19 000)

Fig 4 An altered crista attached *to the outer wall of* a mitochondrion (from the heart of a *patient* who died of rheumatic heart disease (*Case 8A*) (×80 000)

Fig 5 Typical outer membrane alterations in swollen mitochondria (from the heart of a patient who died from a ruptured *aortic aneurysm* Case 6A) (×108 000)

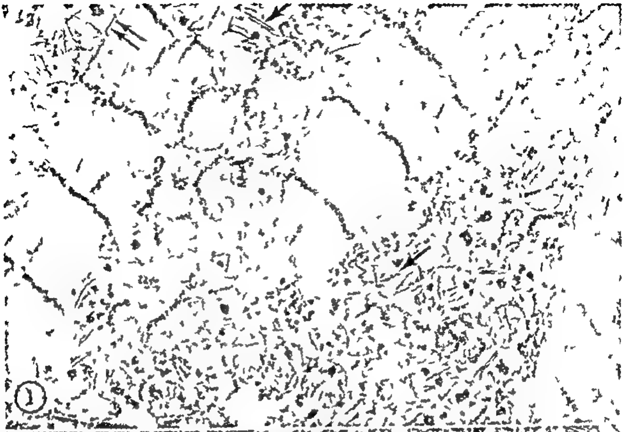

Fig 1 Heart sample taken [illegible] hours after death from a patient who died of alcoholic cardiomyopathy (Case 5A) At least 50 per cent of the mitochondria have membrane alterations both in the rim (double arrow) and in cristae (single arrow) Characteristic autolytic changes are present clumping of chromatin glycogen depletion mitochondrial swelling cristae disruption and granule formation Numerous lipofuscin granules are in the perinuclear region (×12 000)

Fig [illegible] Surgical biopsy specimen from [illegible] patient operated upon for left ventricular aneurysm (Case 7) Note the altered cristae There [illegible] some mitochondrial swelling and cristae disruption but ischemic changes are mild (×20 000)

intermembrane deposits to be continuous also Cristae with the alteration are sometimes attached to the outer membrane (Fig 4) Alterations were not limited to areas of glycogen depletion (Figs 5 and 8)

Discussion

An alteration in the inner membrane space of mitochondria in human myocardium is clearly associated with autolysis The fact that it does not take place in all autopsy specimens and to the same degree after similar periods of time is puzzling Its presence in surgical biopsies leads to speculation that perhaps this change represents a premortal alteration of myocardium Since it has been observed even in one study using perfused cardiac muscle cells of rats[3] it is improbable that it is entirely an autolytic change We were unable to demonstrate a direct correlation between ischemic changes and inner membrane alteration or between hypertrophy and inner membrane alteration

In addition to heart muscle mitochondria this alteration has been demonstrated in skeletal muscle mitochondria including conditions of induced hypertrophy and in kidney mitochondria but it has been sought and not found in liver mitochondria [2] This leads to speculation that differences exist in the composition of mitochondria from different tissues Even if this membrane alteration is a degenerative change its uniqueness to mitochondria from specific tissue may prove to be a valuable aid in the study of mitochondrial function

What is the material deposited between the inner and the outer mitochondrial membrane? One immediately thinks of calcium as Ca ions play an important role in the contraction and relaxation of muscle Calcium deposits in membranes have never been shown to be an ultrastructural feature in studies involving calcium metabolism Loading mitochondria with calcium results in a needle like deposit in the matrix rather than membrane deposits[2] The single dense midline resembles a unit membrane at times but in the preparation of beef heart mitochondria by Saito and associates[10] it was only 30 A wide too narrow to represent the unit membrane In bean root mitochondria the center line is faint Several authors[1,2] have demonstrated periodicity in the inner structure and Wakabayashi and associates induced a lattice structure in inner membrane deposits by treating mitochondrial preparations with phosphotungstic acid A protein deposit is consistent with a substance having periodicity and a lattice structure

This mitochondrial membrane alteration has not been commonly observed We report its presence for the first time in human myocardium It is usually present in autopsy specimens and can be found in some surgical specimens if they are carefully searched It may be an artifact but may on the other hand represent a metabolic alteration that manifests greater effect in some individuals We think it is worth studying because it may represent a functional alteration Perhaps it represents a response to injury Although our results are preliminary and not based on a statistical analysis they nevertheless indicate variations in membrane alterations which cannot be explained solely as a postmortem change

Summary

An alteration consisting of widening of the inner membrane space (approximately 240 A) of the human heart mitochondria was studied and compared in surgical and autopsy material The presence of these changes in well preserved surgical material suggests that it may be a morphologic manifestation of an unknown biochemical alteration

We wish to thank Dr Hugh McAllister from the AFIP for giving us a sample of "stone heart" muscle (Case 9A) We also wish to thank Drs J Titus and J T Lie (Department of Pathology Baylor College of Medicine) for their suggestions and encouragement

Figs 6 and 7 Surgical biopsy of a heart that had developed the stone heart syndrome (Case 10)
Fig 6 Material between the inner and outer mitochondrial membrane appears to push the membranes apart (× 197 000)
Fig 7 A suggestion of periodicity is present (× 208 000)
Fig 8 Autopsy material from the heart of a patient who died of the stone heart syndrome (Case 3A) Glycogen is seen around a mitochondrion showing the membrane alteration (× 105 000)

Figs 6 7 and 8 For legends see opposite page

Single right-sided precordial lead in the diagnosis of right ventricular involvement in inferior myocardial infarction

Leif R Erhardt
Andreas Sjogren
Inger Wahlberg
Stockholm Sweden

Acute myocardial infarction (AMI) is mainly a disease of the left ventricle infarction of the right ventricle is considered rare Isolated right ventricular infarction (RVI) has been found in 2 5 per cent[1] and in 4 6 per cent in autopsy studies of myocardial infarction whereas RVI as an extension from left ventricular infarction (LVI) occurs more commonly RVI is probably more common than previously thought however as evidenced by a recent autopsy study in which transverse heart slicing and enzyme staining were employed revealing RVI in 43 per cent of the patients

In the literature small attention has been paid to the clinical aspects of RVI and it is mostly during later years that papers have appeared concerning its diagnosis hemodynamics implications and treatment Some authors have considered hemodynamic evaluation a mainstay for the diagnosis whereas others have studied the ECG but not found it useful in this respect which may have hampered further studies

In addition to conventionally used precordial CR ECG leads a right sided chest lead CR R has been recorded routinely in our hospital CR leads have been used because these have been routinely employed in preference to V leads in this hospital in recent years In the autopsy study by Erhardt ST segment elevation in Lead CR R was a common finding in patients with RVI as an extension from inferior LVI but was a rare and unspecific finding in anterior LVI with extension to the anterior right ventricular wall

The purpose of the present investigation was to evaluate the diagnostic significance and clinical consequences of ST segment elevation in Lead CR R in patients with inferior LVI in a larger patient group

Patients and methods

All patients were treated in the CCU of Serafimerlasarettet from July 1972 through March 1974 A total of 98 patients with acute transmural inferior myocardial infarction were investigated Six patients were excluded two on account of complete right bundle branch block two on account of complete heart block and two because of differing ECG interpretations among the authors thus leaving a study group of 92 patients There were 22 women and 70 men of whom 18 died (mean age 71 years) and 74 survived (mean age 61 years)

The electrocardiographic (ECG) criteria of acute transmural inferior myocardial infarction were the appearance of a pathological Q wave and the appearance of a local ST elevation followed by T inversion in Leads II III and aV_F Admission criteria serum enzyme diagnostics and policy of treatment have been published previously Twelve lead ECGs (I II III aV_R aV_L aV_F CR_4R $CR_{1,2,4,5,7}$) were routinely recorded on admission and every subsequent morning for days and additionally if indicated clinically The CR R electrode was placed in the fifth intercostal space in the right midclavicular line and ST elevations of more than 1 mm in this lead in any

From the Dept of Med ... Karolinska Institutet Serafimerlasarettet, Stockholm Sweden.

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Reprint requests Dr Inger Wahlberg, Department of Medicin Karolinska Institutet Serafimerlasarettet Stockholm 112 83 Sweden (Box 12700)

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Table I Relation between ST segment elevation in Lead CR R and right ventricular infarction found at autopsy in 18 patients with acute inferior left ventricular myocardial infarction

	No RV involvement (n = 5)	*Minor RV involvement (n = 6)*	*Major RV involvement (n = 7)*
ST-segment elevation	0	2	7
No ST-segment elevation	5	4	0
% ST segment elevation	0	33	100

Table II ST segment elevation in Lead CR,R and RVI size in patients with minor RVI

Pt	*Abnormal ST segment elevation in Lead CR R*	*RV involvement infarction size (%)*	*Survival time (days)*
1	+	25	10
2	+	48	2
3	–	10	1
4	–	30	1
5	–	23	9
6	–	15	5

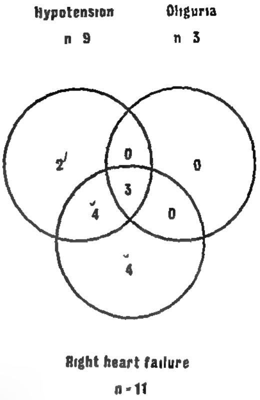

Fig 2 Interrelation between hypotension oliguria, and right heart failure in 16 survivors with ST segment elevation in Lead CR R

coronary artery in 85 per cent as compared to 17 per cent in patients without RVI ($p < 0.05$)

In major RVI the mass of infarcted right ventricular myocardium ranged from 25 to 90 per cent (mean 46 per cent) and survival time ranged from 1 to 21 days (mean 8 days) Corresponding results for minor RVI are shown in Table II In the latter group the time from onset of symptoms to the first ECG was less than 12 hours with the exception of Patient 4 in whom the serum enzyme changes and clinical symptoms suggested that the AMI dated back a couple of days

In the 16 survivors with ST segment elevation in Lead CR R this was present on admission in 13 and was most pronounced on the first day The ST segment rise had usually vanished after 3 days remaining in only one patient The remaining three patients had long lasting chest pains and presented with ST segment elevation on the second day All nine patients with ST segment elevation who died had this on admission

Clinical characteristics in relation to ST segment elevation in Lead CR,R in the survivors and in the deceased are shown in Tables III and IV Hypotension and right and left ventricular failure were significantly more common among the survivors with this ECG pattern whereas no such significances were found when the deceased were compared If survivors and deceased patients are considered together those with an ST segment rise in CR R as compared to those without had a significantly higher incidence of right (76 per cent as compared to 27 per cent $p < 0.001$) and left (96 per cent as compared to 63 per cent $p < 0.01$) heart failure hypotension (68 per cent as compared to 25 per cent $p < 0.001$) as well as oliguria (36 per cent as compared to 9 per cent $p < 0.01$) The interrelation between hypotension oliguria and right heart failure is shown in Fig 2

Serum enzyme determinations permitting the estimation of peak levels were available for all the 74 survivors The survivors with the described ST segment elevation in Lead Cr R had significantly higher peak levels of SGOT (m=258) SGPT

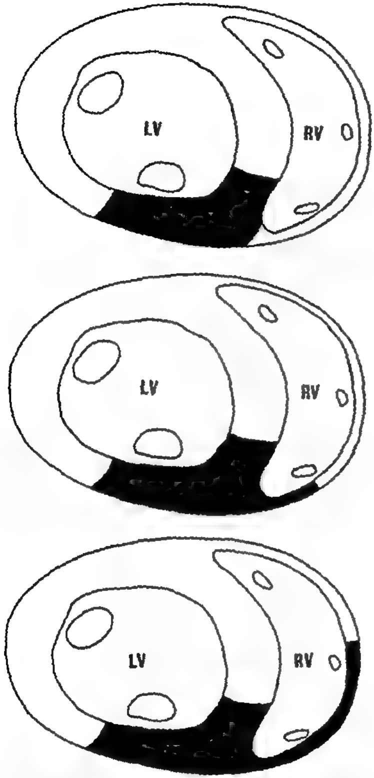

Fig 1 *Pictorial classification of transverse heart slice showing* infarction (black area) Upper Inferior LV infarction without RV involvement Middle Inferior LV infarction with minor RV involvement Lower Inferior LV infarction with major RV involvement

of the ECG s recorded during the first 3 days were classified as abnormal the recordings being checked by the authors separately

Hypotension was defined as a systolic blood pressure of 90 mm Hg or less and oliguria as a urine flow of less than 20 ml per hour Right heart failure was considered present when there were distended neck veins above the level of the clavicle with the patient sitting at a 45 degree angle, or if the central venous pressure (CVP) exceeded 12 cm H 0 Left heart failure was considered present when basal rales were heard on the lungs with or without a third heart sound or when chest x ray showed central or peripheral vascular enlargement, and/or confluent areas compatible with pulmonary edema

At autopsy the heart was examined by a serial transverse slice method[10] and the slices were stained with nitro BT[11] The size of the infarction was estimated by a point counting technique[12] and expressed in per cent of the left and right ventricular myocardium, respectively The stained and nonstained areas were counted, giving the proportion of infarcted to noninfarcted myocardial area After weighing each slice the mass of infarcted myocardium could also be estimated When the area of infarcted myocardium differed markedly on each side of a slice both sides were counted and the mean value was used All autopsies were performed by one of the authors (L R E) and for further details see Erhardt[4] Major infarction of the right ventricular free wall was defined as an extension of the infarction in at least one transverse heart slice to or beyond the lateral margin whereas RVI with less extension was defined as minor (see Fig 1) For the evaluation of the results conventional statistical methods were used

Results

Abnormal ST segment elevations in Lead CR_4R were found in 16 of the 74 survivors and in nine of the 18 deceased patients ($p < 0.025$) The validity of an abnormal ST segment elevation in Lead CR_4R as a sign of right ventricular involvement in acute inferior infarction is given in Table I, in which the autopsy results are presented The patients were divided into three groups major, minor or absence of RVI and they did not differ concerning left ventricular infarction size No patient with purely left inferior ventricular engagement showed an ST segment elevation in Lead CR_4R in contrast to all with major RVI ($p < 0.01$) The patients with minor RVI had this elevation in 33 per cent All patients had some degree of posterior septum infarction which was not related to the size of RVI In patients with RVI a fresh thrombus was present in the right

Table I Relation between ST segment elevation in Lead CR R and right ventricular infarction found at autopsy in 18 patients with acute inferior left ventricular myocardial infarction

	No RV involvement (n = 5)	*Minor RV involvement (n = 6)*	*Major RV involvement (n = 7)*
ST segment elevation	0	2	7
No ST segment elevation	5	4	0
% ST-segment elevation	0	33	100

Table II ST segment elevation in Lead CR,R and RVI size in patients with minor RVI

Pt	*Abnormal ST segment elevation in Lead CR R*	*RV involvement infarction size (%)*	*Survival time (days)*
1	+	25	10
2	+	48	2
3	−	10	1
4	−	30	1
5	−	23	9
6	−	15	5

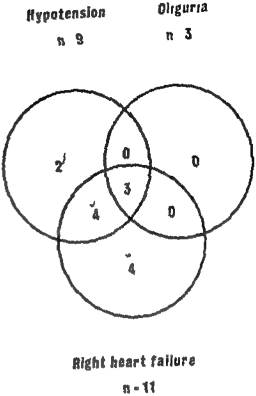

Fig 2 Interrelation between hypotension oliguria and right heart failure in 16 survivors with ST segment elevation in Lead CR R

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Serum enzyme determinations permitting the estimation of peak levels were available for all the 74 survivors The survivors with the described ST segment elevation in Lead Cr R had significantly higher peak levels of SGOT ($\bar{m} = 258$) SGPT

Table III. Clinical characteristics in relation to abnormal ST segment elevation in Lead CR_4R among the survivors (n = 71)

Clinical characteristic	Abnormal CR_4R ST segment elevation: Present (%)	Abnormal CR_4R ST segment elevation: Not present (%)	p
Hypotension	50	19	< 0.05
Oliguria	19	5	N S
Right heart failure	63	21	< 0.01
Left heart failure	91	57	< 0.05

Table IV. Clinical characteristics in relation to abnormal ST segment elevation in Lead CR_4R among the deceased (n = 18)

Clinical characteristic	Abnormal CR_4R ST segment elevation: Present (%)	Abnormal CR_4R ST segment elevation: Not present (%)	p
Hypotension	100	67	N S
Oliguria	67	33	N S
Right heart failure	100	67	N S
Left heart failure	100	100	N S

($\bar{m}$ = 85) and LDH ($\bar{m}$ = 1 230) than those without this elevation ($\bar{m}$ = 170 41 and 750, respectively) ($p < 0.05$).

Discussion

In RVI clinical and ECG diagnostics have previously not been considered sensitive enough for the diagnosis,[11, 14] whereas others have suggested that RVI may be visualized by changes in precordial leads reflecting the right ventricle, i.e., V_1 to V_4.[11, 19, 21] According to our findings a major RVI can be recognized by an abnormal ST segment elevation in Lead CR_4R in patients with acute transmural inferior left ventricular myocardial infarction. It must be stressed that this finding is valid only in the absence of anteroseptal infarction which may interfere with the ECG interpretation concerning RVI (see Fig. 3).

Earlier autopsy studies[4, 11, 1] have mostly reported involvement of the posterior right ventricular free wall accompanying inferior LVI with ECG signs typical for diaphragmatic wall infarction. As the right ventricle and the inferior left ventricle wall are usually both supplied by the right coronary artery, this is to be expected. Myers and associates[11] suggested that great difficulty could be anticipated in the ECG differentiation between septal and right ventricular infarction since the former may also be manifested by changes in the precordial leads over the right ventricle. In the present study, however, the ST segment elevation in Lead CR_4R was not seen in any of the five patients with posterior septal infarction without right ventricular engagement.

Although our present finding of ST segment elevation in Lead CR_4R in RVI could be influenced by the position of the heart in the chest as well as by the transient nature of ST rises in AMI, all patients with major right ventricular involvement showed this pattern. Thus both extension and mass of the RVI seem to be of great importance for the ECG diagnosis. Furthermore, all but one of the deceased patients with more than 25 per cent of the right ventricular mass engaged showed ST segment rise in Lead CR_4R. The exception was a patient with onset of symptoms 2 days before admission in whom the absence of this rise may be explained by the transient nature of the ST segment elevation,[21] as this had vanished after 2 to 3 days in our study. Extension of the infarction from the inferior wall beyond the lateral margin of the right ventricle was found in seven of the nine deceased with ST segment elevation in Lead CR_4R which could mean that not only mass but also location of the infarction is of importance for the ECG changes.

Our present study does not allow conclusions as to possible ECG changes caused by isolated RVI involving the lateral margin. Furthermore, it cannot be excluded that right sided precordial leads other than CR_4R are more revealing in the diagnosis of RVI. However, preliminary results from a study presently performed in our CCU with a further four right sided chest leads, i.e., CR_3R, CR_5R, and two leads placed one intercostal space above and below CR_4R, respectively, do not suggest that much is to be gained by additional leads.

Correlation between infarction size and peak enzyme levels, usually SGOT and LDH_1, has previously been described,[2] and in the present study ST segment rises in Lead CR_4R were corre-

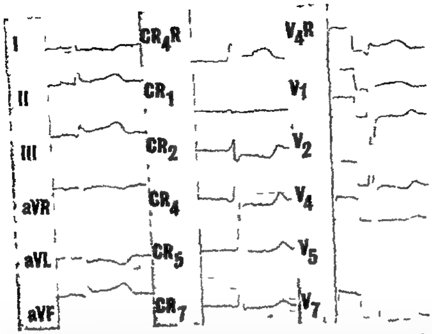

Fig 3 Representative ECG showing ST segment elevation in Lead CR R in a patient with acute inferior infarction V leads have been added for comparison This patient had the following hemodynamic data RV pressures 24/1? and pulmonary artery 20/10 mm Hg on the first day with a subsequent further increase in right sided filling pressures There was hypotension and there were long periods of oliguria requiring furosemide doses exceeding 500 mg daily Paper speed 50 mm per second

lated to higher SGOT and LDH peak values which suggests greater infarction sizes perhaps in part due to the additional damage of the right ventricular myocardium

Cohn and associates suggested that a unique clinical and hemodynamic syndrome arises when LVI is accompanied by RVI Their six patients presented clinically with engorged neck veins hypotension and heart block and hemodynamic measurements disclosed that the right ventricular filling pressure equalled or exceeded left ventricular end diastolic pressures Others have also shown this hemodynamic pattern The findings in the present study of an association between this ST segment elevation in Lead CR R and hypotension and right and left heart failure are in accordance with these studies (Table III) Several of the patients with these ECG findings however failed to show clinical signs of this hemodynamic pattern This may have been due to diuretic therapy in some cases yet it needs pointing out that little is known of the hemodynamic consequences of infarction of the free right ventricular wall per se Septal and right ventricular papillary muscle infarction which often accompanies RVI may also be of major importance and the added afterload due to concomitant left heart failure may also affect right heart performance

According to our results ST segment elevation in Lead CR R implies poor prognosis as to short term survival and early recognition of RVI could be vital This is compatible with the low incidence of old RVI previously reported at autopsy

In conclusion our findings lend support to the following

1 An ST segment elevation of more than 1 mm in Lead CR R indicates right ventricular involvement in patients with transmural acute inferior myocardial infarction

2 This ST segment elevation indicates right ventricular myocardial damage exceeding 25 per cent or reaching the lateral margin of right ventricular free wall

3 Patients with the above ST segment elevation often develop hypotension oliguria and right and left heart failure and have poor prognosis as to short term survival

Summary

The ST segment in a single right sided chest lead CR R has been studied in 92 consecutive patients with acute inferior transmural left ven

tricular myocardial infarction A transient ST segment rise of more than 1 mm was recorded in 25 patients, and strongly indicated a significant extension of the infarction to the posterior free right ventricular wall according to autopsy findings This ECG pattern was furthermore associated with right sided heart failure, hypotension and oliguria Left heart failure was also common The short term prognosis of patients with ST segment elevation in CR,R was poor

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Relative insensitivity of isovolumic phase indices in the assessment of left ventricular function

S Z Naqvi M D F R C P (C)
A W Chisholm M D F R C P (C)
J R Standen M D F R C P (C)
S J Shane M D F R C P (C)
Toronto Ontario Canada

Several recent publications have empha sized the value of derived isovolumic phase indices (contractility indices) in the measurement of ventricular performance Since ventricular function curves (pump function indices) have widely recognized limitations in the assessment of myocardial performance it has generally been considered that the isovolumic phase indices are more sensitive than such curves in the distinction between normal and impaired myocardial func tion

In an attempt to test this thesis we compared indices derived from high fidelity left ventricular pressure recordings and left ventricular cinean giograms with left ventricular function curves The latter were constructed from measurements of left ventricular end diastolic pressure (LVEDP) and stroke work index (SWI) obtained both at rest and after isometric handgrip exer cise

Methods and materials

In this study 20 patients underwent full dress right and left heart catheterization with intra muscular diazepam 5 mg as premedication Retrograde left heart catheterization was per formed by the Seldinger technique Left ventric ular pressures were recorded by a Statham SF 1 catheter standardized against signals from a Statham P 23 Db Pressure Transducer connected to the fluid filled lumen of the same SF 1 cathe ter Simultaneous left brachial artery pressures were recorded using a short No 8 Fr Teflon catheter

The first derivative of the left ventricular pres sure (dp/dt) was recorded by a Resistance/Ca pacitance differentiating circuit (Electronics for Medicine White Plains N Y) with a corner frequency of 160 Hz All pressures were recorded at a paper speed of 200 mm per second Cardiac output was determined by the dye dilution tech nique injecting 5 mg of indocyanine green into the pulmonary artery, and sampling from the left brachial artery catheter The patients then did 3 minutes of isometric handgrip exercise using a Jamar Hand Dynamometer PC 5033) at one third maximum voluntary effort being at the same time discouraged from performing a simultaneous Valsalva maneuver Pressure recordings and cardiac output determinations were repeated at the end of 3 minutes The SF 1 catheter was then replaced by a No 8 Ducor Cordis pigtail catheter and a left ventriculogram was performed in the RAO projection at 60 frames per second Reno grafin 76 (18 ml) was injected during the diastolic filling period for three consecutive cycles with a Viamonte Hobbs Model 2000 Pressure Injector The QRS complex of the electrocardiogram (ECG) was used to trigger the pressure injector The ejection fraction (EF) was calculated from the uniplane ventriculogram by the method of Green and associates Only the first three beats were used in this calculation since Carleton[4] had

From the Division of Cardiology the Department of Radiology and the Cardiovascular Investigation Unit Sunnybrook Hospital Toronto Ontario Canada.

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Reprint request Dr S. J Shane Cardiovascular Unit Sunnybrook Hospital, 2075 Bayview Ave Toronto Ontario Canada M4 1A9

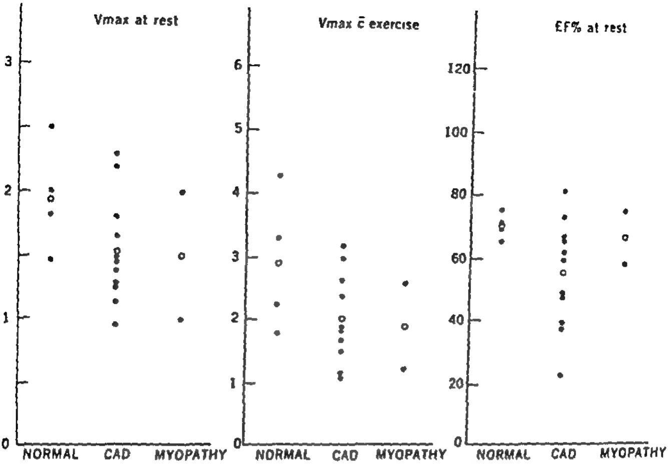

Fig 1 Ejection fractions Groups I and II

shown changes in the left ventricular volume after the second cardiac cycle following opacification The presence of akinetic segments was taken into account and corrections were made for the EF by the method of Kitamura and associates[7]

Percentage shortening of the minor axis was calculated as the change from diastole to systole in those patients free of localized abnormalities of left ventricular function

Peak dp/dt was calculated by multiplying the height of the curve obtained through the R C circuit by the constant (K) of that particular SGM pressure channel and the SF1 transducer

Velocity of contractile element (VCe) was calculated from the expression dp/dt/32P during the period of isovolumic contraction at 5 msec intervals VCe was then plotted against simultaneous left ventricular pressure and the descending limb extrapolated to obtain Vmax in muscle lengths per second (M L /sec) at zero load

VCe and peak dp/dt (Vpm) were calculated using a constant K of 32 at rest and, in 15 patients under the stress of 3 minutes of isometric handgrip exercise

Patient groups Of the 20 patients studied four were found to be normal as judged by resting LVEDP EF Vmax, left ventricular function curves and the left ventriculogram These were placed in Group I Group II consisted of two patients with elevated resting LVEDP One of these had a normal Vmax at rest as well as a normal VCe peak dp/dt and EF, but responded to exercise by an 8 mm Hg rise in LVEDP thus increasing the stroke volume index and the stroke work index The left ventriculogram showed left ventricular hypertrophy The second patient in this group had an elevated LVEDP low normal EF and VCe at peak dp/dt and a decreased Vmax His response to exercise was a decrease in the stroke volume index despite a 7 mm Hg rise in LVEDP The left ventriculogram showed generalized hypokinesia These two patients had normal coronary arteries and a diagnosis of cardiomyopathy was made Group III consisted of 14 patients with proved coronary artery disease

Results

Ejection fraction (EF) Of these 20 patients the left ventriculogram was of unsatisfactory quality for the determination of EF because of runs of VPBs in only two

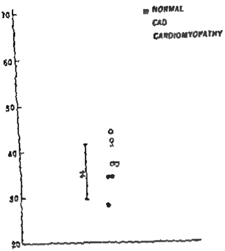

Fig 2 Per cent minor axis shortening.

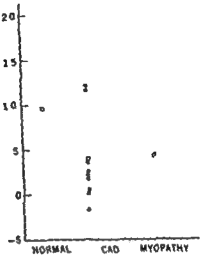

Fig 3 Vmax E R

Patients in Groups I and II had normal ejection fractions (Fig 1) Only five of the 14 patients with coronary artery disease had decreased EF's There was also considerable overlap between the groups and the difference between the means was not statistically significant

Only three of the patients with coronary artery disease showed less than 30 per cent shortening of the minor axis There was considerable overlap between the values of Groups I II and III (Fig 2)

Vmax at rest When compared to the normal value of 1 85 ± 0 26 M L /sec all patients in Group I and one of the two patients in Group II had normal values at rest Only four of the patients in Group III had decreased values at rest There was considerable overlap between the normal subjects and the patients with coronary artery disease with no statistically significant difference in the mean values (Fig 1)

Vmax with exercise In 16 patients Vmax was obtained following isometric handgrip exercise In three patients catheter movement artifact resulting from tachycardia prevented accurate analysis of isovolumic contraction In one patient the resting LVEDP was very high and the response to exercise was not studied

All patients in the normal group showed an increase in Vmax with no more than a 4 mm increase in LVEDP One of the patients in the cardiomyopathy group was able to increase the Vmax by 0 5 muscle lengths (M L /sec) with the assistance of an 8 mm increase in LVEDP The second patient in this group showed an increase in

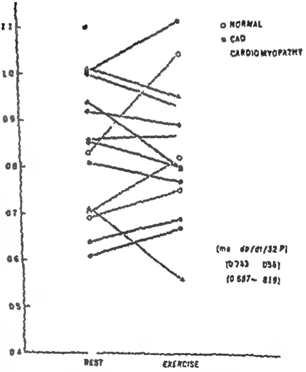

Fig 4 VCe at peak dp/dt

Vmax by 0 15 M L /sec following a 7 mm increase in LVEDP

Patients in Group III demonstrated differing responses to exercise e g an inability to increase Vmax despite inordinate rises in LVEDP One patient had a small increase in Vmax despite a 1 mm fall in resting LVEDP The other patients in this group who were able to increase their Vmax however did so with the assistance of an

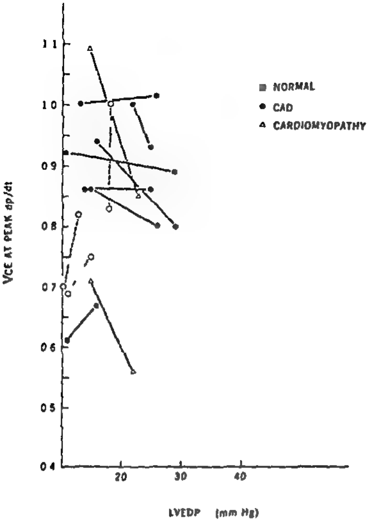

Fig 5 LVEDP plotted against VCe at peak dp/dt

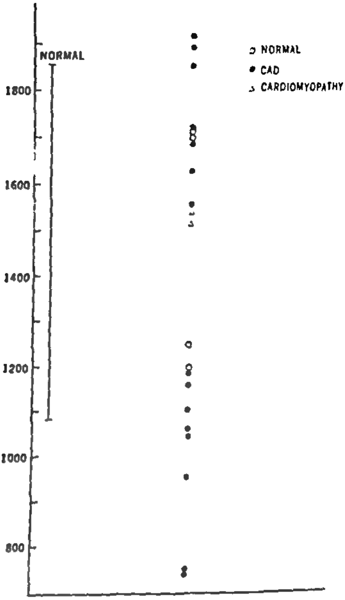

Fig 6 Peak dp/dt resting

increase in LVEDP greater than 4 mm Hg (average 9 6 mm) Although some overlap occurred between the various groups in the mean values of Vmax with exercise there was a significant difference in the values for Vmax with *exercise minus rest* This aided in separating patients with coronary disease from normal subjects (Fig 3)

VCe at peak dp/dt Only five patients with coronary artery disease had a clearly abnormal VCe at peak dp/dt Two of these were able to produce minimal increases in this parameter with isometric handgrip exercise one of them showing a very good response All the remaining patients with coronary artery disease had a fall in the stress induced VCe when compared with their resting values The same was true for the two patients with primary myocardial disease (Fig 4) Left ventricular function curves were constructed with VCe at peak dp/dt plotted against LVEDP and the separation among the three groups became still more striking (Fig 5)

Peak dp/dt As seen in Fig 6 peak dp/dt itself is not a very sensitive index for the separation of normal subjects from patients with cardiomyopathy and coronary artery disease

The construction of left ventricular function curves by plotting peak dp/dt against LVEDP did not make this index any more sensitive than when viewed alone (Fig 7)

Left ventricular function curves Separation was possible among the three groups by the construction of left ventricular function curves (Fig 8) The sole exception was one patient in the normal group in whom catheter entrapment occurred following exercise causing the exercise LVEDP to be spuriously elevated This patient increased his Vmax from 2 5 to 4 3 M L /sec and had a resting LVEDP of 12 mm Hg with an ejection fraction of 76 per cent

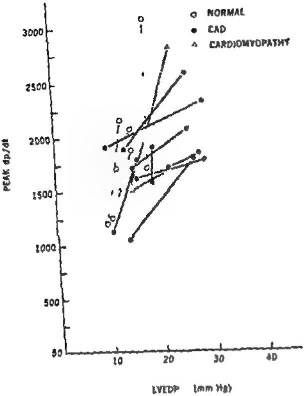

Fig 7 LVEDP plotted against peak dp/dt

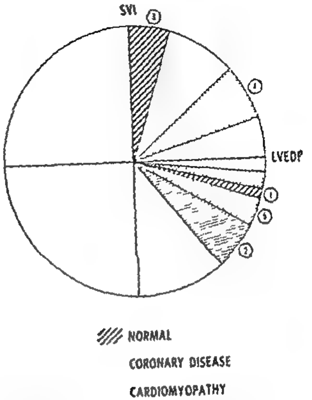

Fig 8 Distribution of LV function curves in three groups of patients. Figures in open circles denote number of patients in each group

Discussion

Many excellent papers have been published in recent years purporting to differentiate reduced hemodynamic performance as a result of mechanical lesions from that due to depressed myocardial function While these have undoubtedly added to our understanding of this subject they have raised many fundamental questions It seems that many other factors have to be taken into account when concepts of muscle mechanics are used to assess contractility in the intact heart and some of our present assumptions appear to be unjustified or unproved This applies to the values for K and c in the formula for VCe Similarly doubt has been raised concerning the original conclusion that Vmax is independent of fiber length. Moreover variations in heart rate alter performance per stroke and the inotropic state directly via force frequency relations Further alterations in aortic pressure alone can greatly influence left ventricular performance

The value of isovolumic phase indices was initially believed to reside in the fact that they were relatively uninfluenced by alterations in preload and afterload but were sensitive to alterations in the inotropic state In our experience peak dp/dt was not sufficiently sensitive in separating normal subjects from patients with coronary artery disease or cardiomyopathy (Fig 6) Ross and associates had previously shown that dp/dt was more sensitive to changes in inotropic state than dp/dt/40 or peak dp/dt/developed pressure In an attempt to narrow the gray zone where overlap was noted in the values of peak dp/dt we introduced the stress resulting from isometric handgrip exercise

As seen in Fig 7 left ventricular function curves were constructed Two patients with coronary artery disease increased their peak dp/dt with only minimal changes in LVEDP overlapping the response shown by normal subjects All the other patients with coronary artery disease and the two patients with cardiomyopathy were able to increase their peak dp/dt only by very significant increases in LVEDP

The technique of plotting VCe against LVEDP (Fig 5) is much more helpful in separating the three groups of patients The abnormal respond

ers showed either a minimal increase in VCe with significant increase in LVEDP or an actual decrease following isometric handgrip exercise—a finding previously reported by Krayenbuhl and associates. That worker suggested that this finding may be the result of the absence of immediate changes in contractility in patients with coronary artery disease. Falsetti and associates[1] had previously reported an absence of significant correlation between VCe at peak stress and the clinical state. In our hands resting values were not helpful in the distinction between normal subjects and patients with coronary artery disease or cardiomyopathies; however, the difference between exercise minus resting Vmax was of discriminative value. Peterson and associates[1] had found that Vmax calculated from total pressure was quite sensitive in separating normal from abnormal subjects although he too noted an overlap when the individual cases were compared. Falsetti and associates[1] found Vmax to be a sensitive and consistent indicator of myocardial performance.

In our experience ejection fraction has not been sufficiently sensitive to separate normal from abnormal subjects (Fig. 1). It has been reported that the ejection fraction may remain normal while the mean Vcf is diminished in mitral regurgitation.[1] Earlier studies had indicated that velocity of wall motion provides a sensitive index of myocardial contractility in the presence of aortic valve disease.

Peterson and associates,[1] using electromagnetic probes, found that peak velocity of shortening provided the best index for the identification of depressed myocardial function. In our hands there was considerable overlap in percentage of minor axis shortening between various groups of patients and this has also been the experience of Karliner and associates.[1] Benzing and associates[1] have recently shown that control of preload and afterload is an indispensable prerequisite in the assessment of the ability of velocity of fiber shortening (Vcf) to reflect changes in the contractile state of the left ventricle.

As seen in Fig. 8, left ventricular function curves were adequate for the separation of normal subjects from patients with cardiomyopathy and coronary artery disease, an experience shared by Swan[1] and by Gorlin and associates.[11] It must be remembered, however, that they do not provide a measure of the inotropic state of the myocardium, and that they are influenced by resting fiber length (preload) and by alteration in wall forces during ejection (afterload). The relative independence of both total and total pressure isovolumic indices from the effect of acute changes in preload remain somewhat controversial.

The experience of Peterson and associates[1] is similar to ours in that we both have found isovolumic phase contraction indices to be unreliable for comparing patients with normal hearts from those with myocardial disease. Some observers consider that the overlap seen in these isovolumic indices may be related in part to as yet unsupported assumptions concerning heart size and series elasticity. Some of the other problems at present disregarded in the determination of contractility have been elegantly summarized by Noble and much further work needs to be done.

Summary

1. The authors compared the sensitivity of the isovolumic phase indices (contractility indices) against LV function curves ("pump function" indices) in assessing ventricular performance.

2. Certain modifications of the usual isovolumic phase indices, especially those introducing the concept of comparison of exercise with rest, seemed to us to be slightly more helpful in separating normal subjects from the patients with coronary artery disease or cardiomyopathies, but these differences were not striking when statistically evaluated and could not be utilized in the assessment of left ventricular function in individual patients.

3. The construction of left ventricular function curves in our hands yielded equally as satisfactory information and, in addition, was much simpler to perform.

4. It is concluded that contractility indices are relatively insensitive in the assessment of left ventricular function and that they offer little advantage over "pump function" indices for this purpose.

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Korotkoff sound filtering for automated three-phase measurement of blood pressure

Alan H Maurer M D
Abraham Noordergraaf, Ph D
Philadelphia Pa

Ever since Korotkoff[1] first proposed auscultation of the sounds which bear his name, the use of the stethoscope and air inflated arterial occlusion cuff has become the most widely accepted technique for the indirect measurement of blood pressure

Attempts at automating auscultatory measurement of blood pressure have led to a proliferation of devices for the detection and processing of the Korotkoff sounds Various authors[2-6] have chosen to look at different portions of the spectrum of these sounds Most have achieved good success at measuring the systolic pressure but poor results have been obtained in measuring diastolic pressure Most investigators in fact have ignored completely the long standing problem of recording both the phase IV (muffling) and the phase V (disappearance) indications of diastolic pressure as currently recommended by the American Heart Association With mounting interest in mass screening of arterial blood pressure it has become apparent that the technique for automated blood pressure measurement must be standardized

This paper describes the filter characteristics which resulted from the development of a system capable of detecting phases I IV and V of the Korotkoff sounds[7] This effort has led to identification of the changes in the Korotkoff sounds that are of importance in auscultation It will be shown that there are changes in frequency content both within and without the range of the stethoscope With the quantification of these changes the use of the Korotkoff sounds in the indirect measurement of blood pressure can now be more precisely defined

The Korotkoff sounds

Although the shortcomings of the Korotkoff technique have been known for some time, it is surprising that to date no accepted theory exists which fully explains the origin of the Korotkoff sounds Korotkoff[1] believed they resulted from the slapping of the arterial walls as the pulse wave of blood slipped through Gittings[8] thought the sound resulted from the sudden distention of the compressed artery Anliker and Raman[9] theorized that the mechanism involves dynamic instability of a viscoelastic system of tissues These are just a few of the many ideas put forth McCutcheon and Rushmer[4] and Chungcharoen[10] offered good reviews of the literature in this area With all the proposed theories however no one explanation has yet been found that is satisfactory

When blood pressure is measured there are five recognized phases of the Korotkoff sounds[11]

Phase I The period marked by the first appearance of faint clear tapping sounds which gradually increase in intensity

Phase II The period during which a murmur or swishing quality is heard

Phase III The period during which sounds are crisper and increase in intensity

Phase IV The period marked by the distinct

From the Department of Bioengineering University of Pennsylvania Philadelphia Pa

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Reprint requests Dr Abraham Noordergraaf Department of Bioengineering University of Pennsylvania Philadelphia Pa 19174

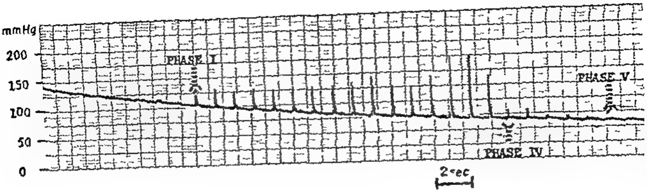

Fig. 1. Example of processed Korotkoff sounds showing selection of phases I, IV, and V.

abrupt muffling of sound so that a soft blowing quality is heard.

Phase V. The point at which sounds disappear.

The rule for measuring systolic pressure has remained the same since Korotkoff first proposed it. The systolic pressure is read as the pressure at which the first sound is heard. The rule for determining diastolic pressure has not remained as consistent. In 1939 the American Heart Association and the Cardiac Society of Great Britain[5] jointly recommended phase IV as a measure of diastolic pressure. Studies after 1939 seemed to contradict this, and in 1951 a committee of the American Heart Association[6] published a report reversing the 1939 recommendation and stating that phase V was considered more reliable than phase IV. The controversy continued, however, and in 1967 the American Heart Association published its latest set of recommendations[2] which advised that whenever possible both the phase IV and phase V pressures should be recorded.

Frequency spectrum of the Korotkoff sounds

Hooker and Southworth[11] were the first to investigate the Korotkoff sounds. In 1914, using crude equipment, they found the predominant frequency to be around 15 Hz. In 1926 Korns[4] described Korotkoff sounds which contained frequencies from 40 to 256 Hz. Others confirmed this general range of frequencies, but it was not until 1965 that Whitcher first emphasized the preponderance of very low frequency information within the Korotkoff sounds. Whitcher demonstrated that the major part of their energy was contained in frequencies below 25 Hz, well below the audible range. These early studies outlined the frequency spectrum of the Korotkoff sounds. They did nothing, however, to characterize the frequency changes that correspond to the systolic and distolic events. McCutcheon and Rushmer[1] showed that the muffling at phase IV could be characterized by an attenuation in amplitude of components in the 60 to 180 Hz range. Such characterization of phases I and V is also essential to provide criteria for automating ausculation of blood pressure and perhaps to yield new insight into the genesis of the Korotkoff sounds.

Electronic detection and processing of the Korotkoff sounds

All systems for electronic detection of the Korotkoff sounds have the same basic elements. A microphone with proper low frequency characteristics is usually contained within the occluding cuff. The output of the microphone is fed into a wide band amplifier which is then connected in series to a filter. This filter is specified by the designer to pass those frequencies which he feels best discriminate the onset, muffling, and/or disappearance of the Korotkoff sounds. Separate filters for each phase may be used. The filtered output is then coupled to an electronic or mechanical device which records the occurrence of phases I and IV or V. These events are then correlated with the pressure in the occluding cuff to indicate systolic and diastolic pressures. More sophistication can be added to such systems. For example, gating the detection of the Korotkoff sounds by timing with the electrocardiogram has been shown to be useful in cancelling out noise artifacts.

Past investigators have chosen different por

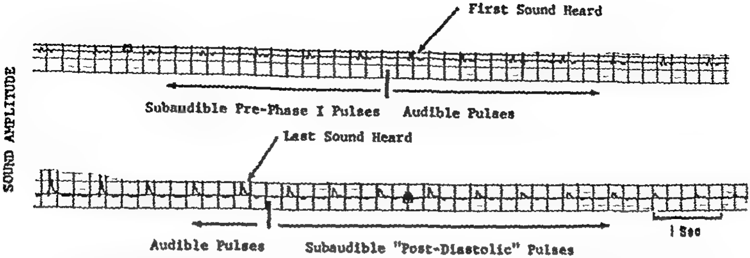

Fig 2 Unfiltered Korotkoff sound recordings (Top) Subaudible complexes are seen well before the onset of the first audible sound (Bottom) Subaudible complexes remain present well after the last sound is heard by the observer

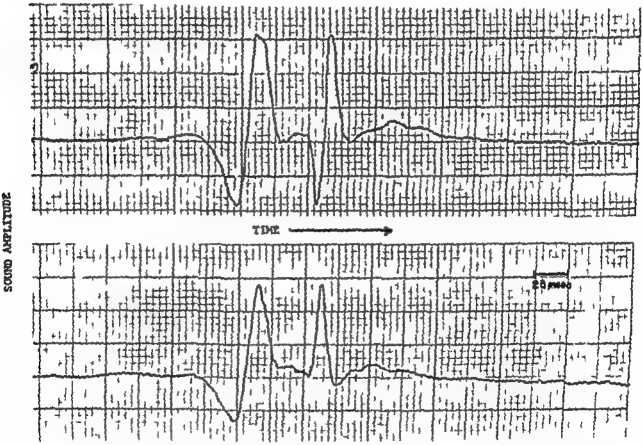

Fig 3 Example of digitized wave forms prepared for computer analysis A final phase III sound (top) is shown compared with the first muffled sound at phase IV (bottom) A loss of high frequency components is evident

tions of the Korotkoff sound spectrum for detection of systolic and diastolic pressures Ware and Kahn[2] used three narrow band filters with center frequencies of 40 90 and 150 Hz for use in the high noise environment of jet aircraft Others chose bandpass filters and looked at a wider range of frequencies London and London[6] used a band pass of 100 to 300 Hz, Davis[3] used a bandpass of 35 to 90 Hz, Canzoneri Geddes Vallbona and Viscusi[4] used a low pass filter with a 3 db slope beginning at 50 Hz It is not possible to compare the results achieved by these authors In most

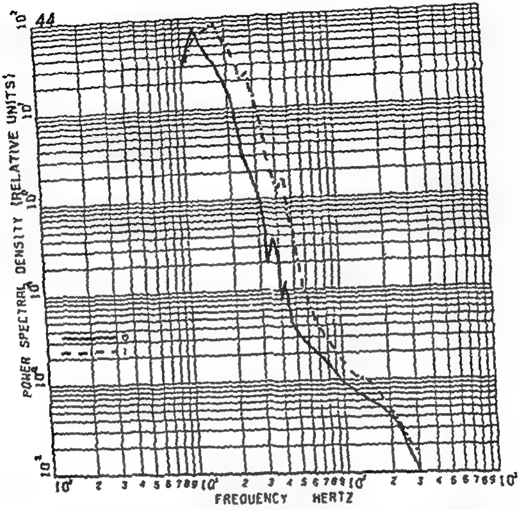

Fig 4 Comparison of the power spectral densities computed for one pair of pre phase I (fully drawn) and phase I sounds Such power spectra display the amount of energy present in each pure tone frequency which contributes to the complete Korotkoff sound complex

cases a different method was used for reporting errors and no distinction between phase V diastolic pressure was made What is clear however is that the authors chose to look at different portions of the Korotkoff sound spectrum in order to measure systolic and diastolic pressures

Methods

Recording technique This paper reports the results of an attempt to better define the changes of Korotkoff sounds that occur at phases I IV and V To do this a low frequency microphone (Rye Industries HB 1) was positioned in an occluding cuff and connected to an FM tape recorder with a frequency response flat from 0 to 5 KHz Blood pressure measurements and Korotkoff sound recordings were taken on subjects who were at rest and seated with the forearm supported at heart level Pressure and sound recordings were done on 155 individuals who were randomly selected from patients who reported to the employees medical clinic in a large private industrial building These subjects included both normotensive and hypertensive individuals A random selection of subjects was desired in order to develop a filter capable of blood pressure measurement in the general adult population

The cuff was manually inflated by the observer who was equipped with a marker switch to indi

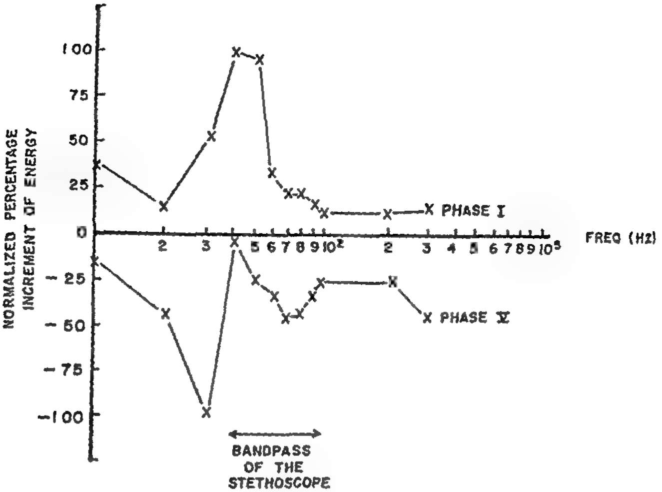

Fig 5 Changes in energy distribution for the Korotkoff sounds at phases I and V The bandpass of the stethoscope is shown for comparison

cate his auscultatory determinations of phases I IV and V using a bell type stethoscope Audiometric testing showed that the observer had normal hearing and the same observer was used in all tests Pressure was released automatically from the cuff at a rate of 2 to 3 mm Hg per second

The Korotkoff sounds were processed by band pass filters which are described below These filtered sounds were then fed to a pulse shaping circuit which displayed on a strip chart recorder all sounds passed by the filter if above a fixed threshold Phase I was taken as the pressure at which the first sound appeared Phase V was the pressure corresponding to the sound which would have followed the last sound recorded Phase IV when present was taken as the pressure corresponding to the sudden drop in amplitude which preceded the disappearance of all sounds (Fig 1)

All sound and pressure data were recorded both on a chart recorder and on magnetic tape The tape was fitted with a time code so that individual sounds could later be identified for analysis

Filter selection It soon became apparent that during a normal blood pressure determination low frequency mechanical vibrations were picked up by the unfiltered microphone well before the observer heard his first sound and that low frequency vibrations continued to be detected well after the observer indicated phase V (Fig 2)

Ertel Lawrence and Song[15] have shown that both the bell type and diaphragm type stethoscopes have similar frequency characteristics with a bandpass of about 40 to 100 Hz The low frequency slope is about 30 db per octave and the high frequency slope is approximately 18 db per octave In the present study these findings served as a basis for the initial selection of a filter which would best correlate electronic detection of the Korotkoff sounds with observer auscultation The recorded sounds were played back through Krohn Hite variable bandpass filters The initial

bandpass chosen was 40 to 140 Hz with low frequency and high frequency slopes of 6 db per octave As previously reported[7] various filter combinations were tried From the results of these trials and the power spectral density analysis to be described a fixed active filter with a bandpass of 50 to 160 Hz and low frequency and high frequency slopes of 48 and 6 db per octave respectively was ultimately chosen to filter the Korotkoff sounds

Characterization of the systolic and diastolic sounds To quantify the key changes occurring at phases I IV and V paired wave forms were singled out for frequency analysis The pre phase I and phase I sounds were located on the magnetic tape and fed unfiltered into a computer which digitized their wave forms into 8 129 samples at a 20 KHz sample rate This also was done for phase III/phase IV pairs and pre-phase V/phase V pairs The sampled sounds were then replotted on an x y recorder to examine their shapes and to insure that each entire wave form had been digitized (Fig 3) With the sounds digitized they were then analyzed by power spectral density analysis (Fig 4) Five sets of recordings selected at random from the 155 subjects were analyzed for the changes at phases I and V The same method was used on data from three other subjects who demonstrated unequivocal muffling at phase IV In order to characterize the phases average percentage changes in energy were calculated at 10 Hz intervals from 10 to 100 Hz and 100 Hz intervals from 100 to 300 Hz These percentages were normalized by setting the maximum at 1 0 (Fig 5)

Results

With the 50 to 160 Hz filter measurement of blood pressure was compared with that of an observer on 155 subjects Agreement on phase I was within ± 5 mm Hg in 97 per cent of the cases Agreement on phase V was ±5 mm Hg in 94 per cent of the cases A distinct phase IV was noted by the observer in 55 per cent of the trials In these cases the filter showed a detectable shift in amplitude 99 per cent of the time

With the 40 to 140 Hz filter agreement on phase I was ±5 mm Hg in 65 per cent of the cases Agreement on phase V was ±5 mm Hg in 67 per cent of the cases No reliable results on phase IV were obtainable

Discussion

It is most informative to look at these results in two areas frequency shifts that occur (1) within the bandpass of the stethoscope and (2) outside the range of the stethoscope

Frequencies within the range of the stethoscope There are three characteristic frequency changes for phases I IV and V that occur within the band of frequencies passed most efficiently by the stethoscope They correspond to the sound changes most audible to an observer listening to the Korotkoff sounds At phase I there is an increase in energy from 20 to 70 Hz with a peak centered at 45 Hz At phase V there is a decrease in energy in the range of 40 to 300 Hz peaking at 70 Hz Golden Wolthuis Hoffler and Gowen[20] have recently reported similar results for phases I and V They report systolic changes from 10 to 50 Hz peaking in the range of 18 to 26 Hz No differentiation was made between phases IV and V in their study but they report 'diastolic changes greatest in the 40 to 60 Hz range which presumably refers to a phase V determination Phase IV is characterized by a loss in energy in frequencies extending from 60 to 300 Hz These results are in keeping with those of McCutcheon and Rushmer[10] cited earlier

More than 90 per cent of the total Korotkoff sound energy is in the spectrum below 25 Hz If all the low frequency energy were passed by the filter it would be difficult to detect the relatively small percentage changes of energy in the frequencies which characterize phases IV and V Since the changes at phase I are maximal within the range of the 50 to 160 Hz filter there is no problem in detecting phase I Almost all of the low frequency energy below the range of the stethoscope is eliminated by using a filter with a bandpass of 50 to 160 Hz and a low frequency slope of 48 db per octave The peak changes that occur within the range of the stethoscope at phases IV and V then account for a greater percentage of the total energy seen by the detection circuitry and recognition of these phases is simplified A system capable of detecting the changes at phases I IV and V results

Frequencies outside the range of the stethoscope The above results suggest that we may at present be ignoring valuable information contained in the subaudible portion of the Korotkoff sound spectrum It has been shown[7] that when a

filter is used which passes more of the low frequency energy peak at 45 Hz, the phase I determinations average 3 mm Hg higher than when a filter more closely matched to stethoscope performance is used Review of the studies that have compared direct blood pressure measurement with ausculation[1] indicates that the auscultatory phase I pressure in the arm is about 5 mm Hg below direct arterial pressure This would suggest that the accuracy of phase I measurements could be improved by considering more low frequency energy No such correlations have yet been made for the peaks that occur at phases IV and V which are also outside the range of the stethoscope

Clinical experience indicates that with hypotension the Korotkoff sounds become inaudible and blood pressure determination unobtainable Whitcher has shown that there is a downward shift in the energy distribution of the Korotkoff sounds in shock In one reported case all measurable sound energy was below 8 Hz After returning to normotensive pressures the energy distribution curve of the patient reverted to a normal pattern

Changes in the high frequency portion of the Korotkoff sound spectrum have also been noted Masuda and Endo and Ware and Anderson have shown that the frequency spectrum of the Korotkoff sounds shifts upward during exercise with a return to normal after rest

At present there is little information on whether frequencies outside the range of the stethoscope yield patterns which are as reliable as those obtained during auscultation at rest Further study of the inaudible components of the Korotkoff sounds may lead to a better understanding of the nature of the Korotkoff sounds to increased accuracy in indirect blood pressure measurement and perhaps to further clinical applications

Summary

Under rest conditions changes in the Korotkoff sounds at phases I IV, and V can be correlated with specific frequencies within the bandpass of the stethoscope A filter capable of detecting the changes in Korotkoff sounds at phases I IV and V is described together with the frequency changes that characterize these phases The importance of frequency components outside the bandpass of the stethoscope is stressed especially in terms of the possibility of yielding more clinical information and, perhaps additional clues about the origin of the Korotkoff sounds themselves

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Formation of coronary arterial thrombi in relation to onset of necrosis in acute myocardial infarction in man

A CLINICAL AND AUTORADIOGRAPHIC STUDY

L. R. Erhardt, M.D.
G. Unge, M.D.
G. Boman, M.D.
Stockholm, Sweden

Several papers on the role of the coronary arterial thrombus in acute myocardial infarction (AMI) have appeared in recent years but opinions still differ as to whether the thrombus precedes or follows the myocardial necrosis.[1-12] The frequent finding of coronary thrombi in patients with transmural infarction, in contrast to subendocardial infarction, is well recognized.[13-17] Coronary thrombosis is, however, neither an exclusive finding nor a requirement for transmural infarction,[18, 19] wherefore its significance for the development of the necrosis can be seriously questioned.

In a previous study the use of [125]I labeled fibrinogen for the timing of thrombus formation in relation to the myocardial necrosis was described.[1] The method used in that study, however, was crude and it was not possible to correlate the incorporation of radioactive fibrinogen with the histologic findings. Therefore an extended study was performed with a refined technique. This study describes radioactivity in coronary thrombi studied by autoradiography in 12 deceased patients admitted to a coronary care unit (CCU) who had been given either [131]I or [125]I labeled fibrinogen routinely for the detection of deep venous thrombosis (D.V.T.).

From the Departments of Medicine, Serafimerlasarettet, and of Thoracic Medicine and Pathology, Karolinska Sjukhuset, Stockholm, Sweden.

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Reprint requests: L. R. Erhardt, M.D., Department of Medicine, Karolinska Institutet at Serafimerlasarettet, S 112 83 Stockholm, Sweden.

Methods

The patients were admitted to the CCU at Serafimerlasarettet, Stockholm, because of chest pain with a defined recent onset. During the study period all patients admitted to the unit for suspected AMI were given approximately 100 μCi of [125]I labeled fibrinogen (Radiochemical Centre, Amersham, England) or [131]I labeled fibrinogen (CEA, Département des Radioéléments, Paris, France) for the detection of D.V.T. Before the injection of labeled fibrinogen the thyroid was blocked with 100 mg. of potassium iodide which was also given daily for another 3 weeks. The criteria for admission to the CCU and policy of treatment have been given elsewhere.[17, 20] Serum enzymes, i.e., SGOT, SGPT, LDH, and LDH_1 (the heat stable portion of LDH) were analyzed on admission and every 12 hours for 3 days, or for longer periods if the patient stayed in the unit because of complications, and twice a week for the remainder of the hospital stay.

Diagnostic 12 lead electrocardiograms (ECG's) were recorded on admission and at least once daily during the stay in the CCU. The criteria for transmural infarction were the appearance of a pathologic Q wave and appearance or disappearance of a local ST elevation followed by T wave inversion in at least two leads. Anterior infarctions were diagnosed by changes in Leads CR_{1-5}

lateral infarctions in Leads I aV_L and CR_7 and inferior infarction in Leads II III and aV_F Combination sites were determined according to the same criteria

At necropsy (L R E) which was performed within 48 hours the heart was examined by serial transverse slicing[21] and the slices were stained with nitro BT[22] The infarction size was estimated with a point counting technique[23] A more detailed description of the autopsy procedure has been given elsewhere[17] The coronary vessels were cut lengthwise When a thrombus was found it was cut in half along its longitudinal axis The thrombus was left adherent to the vessel wall fixed in 10 per cent neutral formalin and mounted in a paraffin block with the cut surface of the thrombus oriented toward the surface of the block If the thrombus was small it was mounted in one paraffin block when the thrombus was longer it was divided into an appropriate number of pieces The embedded material was cut to give a flat surface marked with radioactive ink and apposed to x ray film (Kodirex Kodak) The film was processed after exposure for 2 to 8 weeks No attempts were made to grade the amount of radioactivity which was evidenced by blackening of the film After the autoradiographic procedures sections of the artery and thrombus were made and routinely stained (hematoxylin eosin and van Gieson) Specimens for microscopic examination were also taken from infarcted and noninfarcted regions as well as the border between infarcted and noninfarcted myocardium The age of infarction was estimated from the microscopic findings according to standard criteria[2, 24]

Patients

The study group consisted of 12 consecutive necropsied patients with AMI and coronary thrombosis who had received radioactively labeled fibrinogen There were seven men and five women of ages ranging from 45 to 81 years (mean 67) Five of the patients had a previous myocardial infarction and six patients had angina pectoris (Table I) No patient was on anticoagulant therapy on admission nor was this given during the hospital stay

Results

Clinical and laboratory findings The ECG showed signs of transmural infarction on admission in eight patients (Table II) In two additional patients diagnostic ECG changes were first seen after admission—in one patient (No 8) after 10 hours and in another after 24 hours (No 12) Patient No 12 had a combined right and anterolateral bundle branch block on admission which may have disturbed the ECG diagnosis of AMI

The SGOT (serum glutamic oxalacetic transaminase) value was raised on admission in six of the patients due to a long delay between onset of pain and admission (Table II) One of these patients (No 5) had a history suggesting an infarction several days old and the SGOT pattern probably represented the tail of the enzyme curve The SGOT level rose above the normal level within 12 hours in five of the patients with normal SGOT values on admission and in one patient this occurred after 24 hours The time for the occurrence of the peak enzyme value is given in Table II In one patient with long admission delay (No 9) the highest SGOT value was found on admission and one patient (No 11) died before the estimated maximum was reached In two patients (Nos 1 and 3) it was impossible to decide the time of the maximal SGOT value because of the addition of enzymes from the liver All patients were treated for heart failure The mode of death was considered heart failure or cardiogenic shock in seven patients and five patients died of left ventricular rupture and pericardial tamponade

Table I Age sex and medical history in 12 patients receiving radioactively labeled fibrinogen*

Pt No	*Sex*	*Age*	*History of*				
			AMI	*AP*	*CHF*	*Diabetes*	*HT*
1	M	60	×1	−	+	+	−
2	F	73	−	+	−	+	+
3	M	72	−	−	−	−	−
4	M	79	×1	+	+	−	−
5	M	71	×2	+	−	−	−
6	M	45	−	+	−	−	−
7	F	81	−	−	−	−	−
8	F	55	−	−	−	−	+
9	M	66	×1	+	+	−	+
10	F	77	−	+	+	−	+
11	[illegible]	58	×2	−	+	−	+
12	M	72	−	−	−	−	−

AMI, acute myocardial infarction AP angina pectoris CHF congestive heart failure HT hypertension

Table II ECG findings and changes in SGOT in relation to onset of symptoms in 12 patients receiving radioactively labeled fibrinogen*

Pt No	*Type of injury*	*Site of injury*	*Time of diagnostic ECG change*	*SGOT value on admission*	*Abnormal SGOT level reached*	*SGOT maximum reached*
1	Tm	Ant lat	O a	Raised	–	–
2	Tm	Inf	O a	Raised	–	Within 36 hr
3	Tm	Inf lat	O a	Raised	–	–
4	Tm	Inf	O a	Normal	Within 12 hours	Within 48 hr
5	–†	Ant lat	O a	Raised	–	–
6	Tm	Inf	O a	Normal	Within 12 hours	Within 36 hr
7	Tm	Ant	O a	Normal	Within 12 hours	Within 48 hr
8	Tm	Ant.	10 hr after a	Normal	Within 12 hours	Within 24 hr
[illegible]	Tm	Ant	O a	Raised	–	O a
10	Tm	Ant	O a	Normal	Within 12 hours	Within 36 hr
11	LBBB	–	O a	Raised	–	O a
12	Tm	Ant lat	24 hr after a	Normal	Within [illegible] hours	–

Tm transmural infarction LBBB left bundle branch block Ant anterior Inf inferior Ant. lat anterolateral Inf lat inferolateral O.a *on admission*

†*ST segment depressions only*

Table III Autopsy findings in 12 patients receiving radioactively labeled fibrinogen *

Pt No	*Infarction site: Left ventricle*	*Infarction site: Right ventricle*	*Infarction size: Left ventricle Recent (%)*	*Infarction size: Left ventricle Old (%)*	*Infarction size: Right ventricle recent (%)*	*Heart weight (gm)*	*Location of fresh thrombus*	*Length of thrombus (mm)*	*Distance from aorta to proximal end of thrombus (mm)*	*Presence of stenosis*	*Presence of ulcerated plaque*
1	Ant lat.	Ant	35	5	10	790	LAD	35	30	+	–
2	Inf lat.	Inf	36	–	23	460	RC	25	60	+	–
3	Inf lat	–	22	–	–	410	LAC	10	40	–	–
4	Inf	Inf	25	10	25	610	RC	60	40	+	–
5	Ant lat	–	53	8	–	500	LAC	30	15	+	+
6	Inf †	Inf	49	–	36	520	RC	85	[illegible]	+	–
7	Ant lat‡	–	50	–	–	470	LAD	4	40	+	–
[illegible]	Ant.	–	28	12	–	400	LAD	7	30	+	+
9	Ant †	Ant inf	40	–	84	675	LAD§	30	40	+	+
10	Ant lat	–	55	–	–	400	LAD	8	20	+	–
11	Inf †	–	65	5	–	540	RC	40	[illegible]	+	–
12	Lat	–	35	–	–	400	LAC	[illegible]	30	+	–

*Ant anterior Inf inferior Lat., lateral Ant lat anterolateral Inf lat inferolateral Ant inf anteroinferior LAD left anterior descending coronary artery LAC left circumflex coronary artery RC right coronary artery

†With circular subendocardial involvement

‡With subendocardial extension to the inferior left ventricular wall

§Old thrombus [illegible] DX

Necropsy findings All patients had recent myocardial necrosis with a histologic age that agreed with the clinical estimate of onset of necrosis The infarction was transmural in all patients, in four of them with subendocardial extension (Table III) Three patients had histologic evidence of reinfarction, which was clinically diagnosed in two of them (Nos 5 and 7) In one patient (No 11) the age of necrosis varied from 1 to 7 days in different parts of the infarcted myocardium The site of necrosis at necropsy generally agreed with the location of infarction according to the ECG (Table III) The right ventricle was involved in the necrosis in five patients (Table III) The sizes of infarction in the left and right ventricles, respectively, are given in

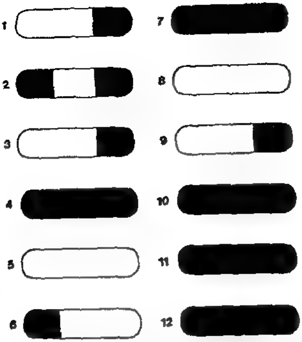

Fig 1 Diagrammatic representation of radioactivity in the coronary arterial thrombi in 12 patients receiving radioactively labeled fibrinogen Black area represents presence of radioactivity Left in the figure is towards the aorta i e the proximal end of the thrombus

Table III In addition to the rupture of the left ventricular wall in the five patients dying of pericardial tamponade there was a septal rupture in one patient and a rupture of the anterior papillary muscle in another patient The heart weights ranged from 400 to 790 Gm (mean 515 Gm) (Table III)

The coronary thrombus was located in the left anterior descending artery in five patients in the left circumflex artery in three patients and in the right coronary artery in four patients (Table III) In patient No 9 there was in addition to the fresh thrombus in the left anterior descending artery also an old thrombus in the right coronary artery The lengths of the thrombi varied from 4 to 85 mm the longest being found in the right coronary artery The distance from the aorta to the proximal end of the thrombus is given in Table III Stenosis at the site of thrombosis was present in all but one patient and an ulcerated plaque was found in three patients The microscopic examination of the arteries and the coronary thrombi verified the gross findings Fresh coronary thrombi with an age that roughly agreed with the age of the myocardial necrosis were present in all patients and there were no signs of different ages in various parts of the thrombi. We recognize however the great difficulty of deciding the exact age of a thrombus

Table IV Type of isotope time intervals and number of autoradiograms in 12 patients receiving radioactively labeled fibrinogen

Pt. No	Type of isotope	Interval between onset of symptoms and injection of fibrinogen (hr)	Survival from injection of fibrinogen (hr)	No of autoradiograms
1	[illegible]I	68	162	2
2	I	73	97	1
3	I	72	74	1
4	[illegible]I	5	249	3
5	[illegible]I	145	21	2
6	I	5	354	5
7	I	6	144	1
8	[illegible]I	65	394	1
9	[illegible]I	50	117	2
10	[illegible]I	7	22	1
11	I	72	5	2
12	[illegible] I	8	90	3

Time intervals and autoradiographic findings Seven patients received ^{125}I labeled fibrinogen and five patients ^{131}I labeled fibrinogen (Table IV) The interval between onset of symptoms and the injection of radioactively labeled fibrinogen varied from 5 to 145 hours and the survival from the time of injection varied from 5 to 394 hours (Table IV)

In all but two patients there was presence of radioactivity in the coronary thrombus (Fig 1) In five patients the entire thrombus contained radioactivity and the interval between onset of symptoms and the injection of radioactively labeled fibrinogen was less than 10 hours in four of them Despite a long interval of 72 hours between onset of symptoms and injection of fibrinogen the entire thrombus was radioactive in patient No 11 The objective parameters for evaluating onset of necrosis in this patient were missing however as the ECG showed a total left bundle branch block and the patient died before several enzyme tests were performed Furthermore the age of necrosis in this patient was not uniform

Table II ECG findings and changes in SGOT in relation to onset of symptoms in 12 patients receiving radioactively labeled fibrinogen*

Pt No	Type of injury	Site of injury	Time of diagnostic ECG change	SGOT value on admission	Abnormal SGOT level reached	SGOT maximum reached
1	Tm	Ant lat	O a	Raised	–	–
2	Tm	Inf	O a	Raised	–	Within 36 hr
3	Tm	Inf lat	O a	Raised	–	–
4	Tm	Inf	O a	Normal	Within 12 hours	Within 48 hr
5	–†	Ant lat	O a	Raised	–	–
6	Tm	Inf	O a	Normal	Within 12 hours	Within 36 hr
7	Tm	Ant	O a	Normal	Within 12 hours	Within 48 hr
8	Tm	Ant	10 hr after a	Normal	Within 12 hours	Within 24 hr
9	Tm	Ant	O a	Raised	–	O a
10	Tm	Ant	O a	Normal	Within 12 hours	Within 36 hr
11	LBBB	–	O a	Raised	–	O a
12	Tm	Ant lat	24 hr after a	Normal	Within 24 hours	–

Tm transmural infarction LBBB left bundle branch block Ant., anterior Inf inferior Ant. lat., anterolateral Inf lat., inferolateral O a on admission
†ST segment depressions only

Table III Autopsy findings in 12 patients receiving radioactively labeled fibrinogen *

Pt No	Infarction site: Left ventricle	Infarction site: Right ventricle	Infarction size: Left ventricle Recent (%)	Infarction size: Left ventricle Old (%)	Infarction size: Right ventricle recent (%)	Heart weight (gm)	Location of fresh thrombus	Length of thrombus (mm)	Distance from aorta to proximal end of thrombus (mm)	Presence of stenosis	Presence of ulcerated plaque
1	Ant lat	Ant	35	5	10	790	LAD	35	30	+	–
2	Inf lat.	Inf	36	–	23	460	RC	25	60	+	–
3	Inf lat	–	22	–	–	410	LAC	10	40	–	–
4	Inf	Inf	25	10	25	610	RC	60	40	+	–
5	Ant lat	–	53	8	–	500	LAC	30	15	+	+
6	Inf †	Inf	49	–	36	520	RC	85	0	+	–
7	Ant lat‡	–	60	–	–	470	LAD	4	40	+	–
8	Ant.	–	28	12	–	400	LAD	7	30	+	+
9	Ant †	Ant inf	40	–	84	675	LAD§	30	40	+	+
10	Ant lat	–	55	–	–	400	LAD	8	20	+	–
11	Inf †	–	65	5	–	540	RC	40	18	+	–
12	Lat	–	35	–	–	400	LAC	25	30	+	–

Ant anterior Inf., inferior Lat lateral Ant lat anterolateral Inf lat inferolateral Ant inf anteroinferior LAD left anterior descending coronary artery LAC left circumflex coronary artery RC right coronary artery
†With circular subendocardial involvement
‡With subendocardial extension to the inferior left ventricular wall
§Old thrombus in DX

Necropsy findings All patients had recent myocardial necrosis with a histologic age that agreed with the clinical estimate of onset of necrosis The infarction was transmural in all patients in four of them with subendocardial extension (Table III) Three patients had histologic evidence of reinfarction, which was clinically diagnosed in two of them (Nos 5 and 7) In one patient (No 11) the age of necrosis varied from 1 to 7 days in different parts of the infarcted myocardium The site of necrosis at necropsy generally agreed with the location of infarction according to the ECG (Table III) The right ventricle was involved in the necrosis in five patients (Table III) The sizes of infarction in the left and right ventricles, respectively, are given in

It has been suggested that the radioactivity found in these coronary thrombi may have been deposited in the thrombus after its formation i e by perfusion[6, 1] This has also been found experimentally in venous thrombi formed within 1 hour prior to the injection of radioactively labeled fibrinogen[27] We cannot exclude that such deposition takes place but it is difficult to explain why this should take place in only one or both ends of the thrombus and why some thrombi failed to contain radioactivity Furthermore we have shown that the radioactive material is found throughout the thrombus and not only on the surface On the other hand a secondary deposition of radioactively labeled fibrinogen might take place only in very fresh thrombi and this could give the same result Thus the controversy regarding the way of incorporation of the radioactivity in the coronary thrombi will have to remain open and the question deserves further experimental investigation

In the present study histologic sections of the thrombi were made which verified the gross findings Thus there was no misinterpretation of coronary thrombi for clots or richly vascularized plaques It should be understood however that transverse sectioning of the arteries is a superior method for microscopic examination

The present study seems to add further evidence that formation of coronary arterial thrombi in AMI is mainly a secondary event However the large red thrombus observed grossly at autopsy is preceded by microscopic changes involving the platelets and fibrin formation is a late sequela rather than a primary event in arterial thrombosis[8] It does not seem inappropriate to assume that in most cases there is an injury to the vessel wall which in some cases leads to an occlusive thrombus but in others will only give a mural thrombus The initial events involving the platelets probably occur very rapidly whereas the formation of the red thrombus ■ a more time consuming process as indicated by the present study Furthermore the myocardial necrosis may in itself facilitate the formation of the red thrombus by giving rise to a stasis in the supporting artery as shown experimentally by Hellstrom

Thus when discussing the significance of coronary artery thrombosis in AMI it must be clear that we know very little about the events before the formation of the large red part of the thrombus and that the triggering of the process finally leading to myocardial necrosis may indeed be vascular and involve platelet aggregation

Summary

The presence of radioactivity in coronary arterial thrombi was studied at necropsy by autoradiography in 12 patients with acute myocardial infarction Seven patients had been given ^{125}I and five patients ^{131}I labeled fibrinogen With a short interval (less than 10 hours) between onset of symptoms and injection of fibrinogen the entire thrombus was radioactive in four of five patients whereas with longer time intervals only parts or none of the thrombus contained detectable radioactivity The findings give further evidence that thrombus formation in acute myocardial infarction probably is a slow process and that the major part of the thrombus may form after the onset of necrosis

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Fig 2 *Left* Autoradiogram of the coronary thrombus in patient No 2 showing radioactivity in both ends of the thrombus The proximal end of the thrombus (towards the aorta) is to the left in the figure (×2) *Right* Histologic section of the coronary artery and thrombus in patient No 2 (×2)

Parts of the thrombus—only the distal end, the proximal end, or both—were radioactive in another five patients The autoradiogram of the thrombus and histologic section of the coronary artery and thrombus in patient No 2 are shown in Fig 2 The time interval between onset of symptoms and the injection of fibrinogen in these five patients was in four of them, 50 hours or more In one patient (No 6) the interval was only 5 hours The ECG was diagnostic of AMI in this patient however the enzyme curve was typical and the histological age of necrosis corresponded to the clinical age of the infarction

In the two patients without detectable radioactivity in the thrombi the time intervals between onset of symptoms and the injection of radioactively labeled fibrinogen were 65 and 145 hours respectively

Discussion

The present study seems to corroborate the previous investigation using ^{125}I labeled fibrinogen for determining the relation between onset of myocardial necrosis and formation of coronary arterial thrombi [1] With a short interval (less than 10 hours) between onset of symptoms and injection of radioactively labeled fibrinogen the entire thrombus was radioactive in four of five patients whereas with longer time intervals only parts or none of the thrombus contained detectable radioactivity Thus, it appears that thrombus formation in AMI takes place over a period of several hours and that the thrombus may grow both proximally and distally, as previously suggested [1]

The radioactive fibrinogen was injected after the onset of infarction in 10 patients according to the clinical and laboratory findings One patient (No 11) had a varying age of the myocardial necrosis according to the histology but unfortunately the clinical and laboratory findings were inconclusive and did not allow the timing of onset of myocardial necrosis The interval between onset of pain and the injection of fibrinogen was as long as 72 hours and the patient survived for only 5 hours after the injection, yet the entire thrombus was radioactive This finding, in combination with the histology in the myocardium suggests that thrombus formation may be a late event in a progressive infarction process

The myocardial infarct in patient No 12 may have occurred after the injection of radioactively labeled fibrinogen although this is unlikely The ECG showed a combined bundle branch block on admission which may have disturbed the interpretation and although the enzyme level was still within normal range after 12 hours the enzyme curve had started to rise The entire thrombus in this patient was radioactive

Despite a short interval between onset of symptoms and the injection of radioactively labeled fibrinogen the thrombus in patient No 6 was radioactive only in the proximal end Histologically there were no differences between the proximal and distal ends of thrombus The thrombus was very long (85 mm) and began at the ostium of the right coronary artery If the thrombus formed slowly in a distal direction the amount of radioactivity in the distal end might be too small to be detected A lower amount of radioactivity toward the distal end of the thrombi was in fact found in five of the seven patients described in the previous study [1] We cannot exclude however that the distal portion of the thrombus was already formed at the time of injection of the radioactively labeled fibrinogen

Experimental and laboratory reports

Ventricular performance measured during ejection. Studies in patients of the rate of change of ventricular power

Paul D. Stein, M.D.
Hani N. Sabbah, B.S.
Oklahoma City, Okla.

The ejection rate of change of ventricular power has attributes which make it advantageous for the evaluation of ventricular performance.[1,2] Its relation to ventricular energy gives it a fundamental fluid dynamic significance as well as a physiological meaning. Its derivation is free of assumptions, the expression therefore being firmly based upon theory. Of a practical nature, the ejection rate of change of power was shown in dogs to be sensitive to drug-induced alterations of the contractile state, yet affected little by alterations of preload or afterload.[2] For these reasons, the ejection rate of change of ventricular power appears to be a hemodynamic expression which merits evaluation in patients.

Methods

Ventricular power is the product of ventricular pressure and flow. The rate of change of ventricular power is derived by differentiation of this product and can be written as follows:[1]

$$\text{Rate of change of power} = Q\,\frac{dp}{dt} + p\,\frac{d\dot{Q}}{dt} \qquad (1)$$

Where p = intraventricular pressure (dynes/cm^2)

$\dot{Q}$ = aortic flow (cm^3/sec) and dp/dt and d$\dot{Q}$/dt are their respective rates of change.

The rate of change of power during ejection was calculated in 22 patients with angina during diagnostic cardiac catheterization. Patients were studied consecutively. All but one of the patients had coronary arterial disease, the severity of which varied; one patient had angina with arteriographically normal-appearing vessels. Patients with valvular disease were excluded. Patients in whom ventricular premature contractions occurred during ventriculography, or in whom reliable aortic velocities were not obtained were also excluded. All patients received light sedation with diazepam (Valium) and were studied in the postabsorptive state.

Velocity was measured at the root of the aorta with a catheter-tip velocity sensor (Carolina Medical Electronics, King, N. C.). A tapered tip distal to the velocity sensor was passed across the aortic valve. This facilitated a reasonably straight alignment of the catheter along the axial stream of flow. It also stabilized the tip of the catheter during diastole, thereby reducing artifact due to motion of the catheter. A sample of original data is shown (Fig. 1). Blood velocity showed some artifact due to 60 cycle interference in spite of the fact that a 30 Hz filter was utilized. However, these were high gain tracings; the deflection of the original data was approximately 6 cm. The important data were derived from the upstroke of the velocity signal which was uniformly smooth and little affected by interference.

The profile of flow was assumed to be flat, and the cross-sectional area of the aorta was assumed to be constant. The velocity signal on this basis would be identical to a flow signal.[3] The flow signal was calibrated by the measurement of cardiac output utilizing the indicator dilution technique with indocyanine green.

From the Department of Medicine, University of Oklahoma College of Medicine and Veterans Administration Hospital, Oklahoma City, Okla.

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Reprint requests: Paul D. Stein, M.D., Veterans Administration Hospital, 921 N.E. 13th St., Oklahoma City, Okla. 73104.

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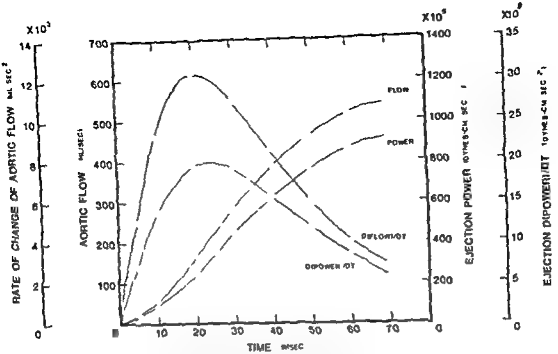


Fig 2 Instantaneous values in a patient with normal ventricular performance of aortic flow rate of change of flow [d(flow)/dt], power and the rate of change of power [d(power)/dt]. Values are shown as a function of time after the onset of ejection. (Patient D B., Table I)

Table I Patients with normal performance (E F > 58 per cent V_{cf} > 1 3 sec ¹ EDVI < 90 cm ³/ M²)*

Patient	Heart rate (b p m)	Blood pressure (mm Hg)	LVEDP (mm Hg)	Cardiac index (L / min / M)	Ejection fraction (%)	V_{cf} (sec)	LVEDI (cm / M)	Peak dp/dt (mm Hg/sec)	Peak (dp/dt) /p (sec)	V max (sec)	Peak flow (cm / sec)	Peak dQ/dt (cm. / sec)	Peak power × 10⁴ (dynes cm./ sec)	Peak d(power) /dt × 10⁶ (dynes cm / sec)
E. S	60	120/77	17	2.8	75	1 7	61	1 400	38	1 49	600	13,000	780	[illegible]
J M	94	130/80	12	3.4	73	1.9	55	1,500	38	1.59	"40	15 000	1 100	23
R. G	72	107/76	7	3 2	0	1.8	84	1,300	37	1 48	,60	19 000	800	27
[illegible] M.	92	128/"0	7	3 3	59	2.5	4?	2 000	67	2.58	8?0	24 000	1,300	39
B F	60	120/77	[illegible]	3 0	85	1 7	83	1,300	32	1.28	1000	21 000	1 600	28
E. P	90	109/68	[illegible]	2 8	65	1.6	69	1,200	48	1 61	630	14 000	830	18
D B	78	146/ 10?	13	2 6	64	2.2	[illegible]	1 400	26	1 20	540	12 000	920	20
R. C	66	10?/62	[illegible]	2 6	66	1 4	61	1,300	35	1.53	930	17 000	1,200	22
B J	10?	140/95	14	2 8	63	2 4	"1	3,200	53	2 15	6.0	14 000	1,280	28
W N	72	128/75	9	2.7	70	1.5	8?	1,300	60	1 5?	600	16 000	8.0	23
Mean	79	123/78	11	2.9	69	1.8	69	1 600	4?	1 64	700	1?,500	1 100	25
± S E.	5	5/4	1	0 1	2	0 "	4	200	4	1	51	1,200	90	2

K y to Table I

E.F = ejection fraction

V_{cf} = mean velocity of circumferential fiber shortening

LVEDVI = left ventricular end-diastolic olume index.

LVEDP = left ventricula end-diastolic pressure

dp/dt = rate of change of left ventricular pressure.

dQ/dt = rate of change of flow

d(power)/dt = rate of cha g f powe

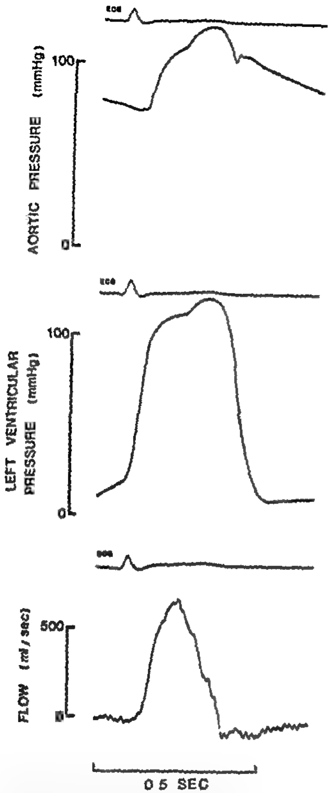


Fig 1 Samples of original data showing aortic pressure (top) left ventricular pressure (middle) and aortic velocity (bottom) The ECG is also shown

Following measurements of flow pressures were measured in rapid sequence with a high frequency micromanometer (Millar Instruments, Inc, Houston, Texas) located at the tip of a cardiac catheter Pressure and flow were recorded on a photographic recorder at a paper speed of 200 mm per second The tracings were digitized with an electronic digitizer (Numonics Corp North Wales Pa) on line with a Hewlett Packard 2100 A computer (Waltham Mass) The equations descriptive of left ventricular pressure and aortic flow were calculated by the Chebyshev polynomial approximation technique as previously described[1] From the computed mathematical equations descriptive of intraventricular pressure and aortic flow, and with the aid of a computer peak values of left ventricular dp/dt rate of change of flow, power and the rate of change of power were calculated* Maximum $\frac{dp/dt}{p}$ was also obtained from the computerized data Vmax was calculated as the linear extrapolation of $\frac{dp/dt}{p}$ plotted with respect to intraventricular pressure[1] Data corresponding to pressures of less than 20 mm Hg was excluded because of inherent inaccuracies related to calculations of the ratios of small numbers

The nonsimultaneous measurement of ventricular pressure and aortic flow would tend to reduce the precision of the measurement of the maximum rate of change of power The maximum rate of change of power occurred during the blunt, slowly changing peak portion of the ventricular pressure curve, which minimized errors due to nonsimultaneous measurements In this investigation, a steady state during the period of measurements was assumed and an effort was made to achieve such a steady state Catheters with a combination of sensors are being developed which would permit simultaneous pressure and velocity measurements Such a catheter utilized with an analogue computer would facilitate use of this index and permit measurements under changing conditions

Both Vmax and maximum $\frac{dp/dt}{p}$ were calculated on the basis of the actual pressure[1,2] All but one of the patients with poor ventricular performance had either hypokinesis, akinesis or dyskinesis Presumably therefore nonuniform contraction also occurred during isovolumic systole in all but one of the patients with

*The technique of the calculation of the peak rate of change of power from the equations descriptive of pressure and flow as described in this study is unnecessarily complex for ordinary clinical usage A dedicated analogue computer would simplify such calculations such a computer is now being constructed

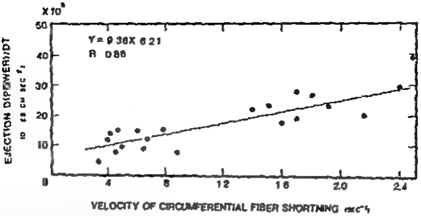


Fig 4 Rate of chang of power [d(power)/dt] measured during ejection shown in relation to the mean velocity of circumferential fiber shortening Correlation coefficient (r) is shown

Table II Patients with abnormal performance (E F 50 per cent V_{cf} 1 [illegible] sec ¹)

Patient	Heart rate (b p m)	Blood pressure (mm Hg)	LVEDP (mm Hg)	Cardiac index (L / min / M²)	Ejection fraction (%)	V (sec)	LVEDI (cm / M²)	Peak dp/dt (mm Hg/sec)	Peak (dp/dt /p) (sec)	V max (sec)	Peak flow (cm / sec)	Peak dQ/dt (cm / sec)	Peak power × 10 (dynes cm./sec)	Peak d(power) /dt × 10 (dynes cm / sec)
R G	84	104/71	13	2.2	?7	0 4	64	1,300	35	1.57	3?0	7 000	400	8
B L	[illegible]	9?/65	20	2.1	2?	0 6	53	1 500	38	1 62	280	6,?00	400	9
R L	?3	110/ 0	10	? 4	46	0 9	108	1 100	30	1 70	290	5 100	380	7
W H	80	115/8?	16	2.4	21	0 6	87	1,200	25	1 36	400	11,000	?00	15
R W	?6	105/74	12	3 0	36	0 7	108	900	23	1 03	600	9 000	6?0	12
R. Y	64	90/63	14	2 2	44	0 6	74	800	25	1 12	350	8,200	390	9
O B	60	100/?0	8	2 7	49	0 4	85	900	33	1 42	5 0	10 000	680	14
L L B	9?	13 /87	15	3 3	36	0 5	[illegible]	1 ?00	49	2 00	490	12 000	700	15
R N	7?	131/88	15	2 6	38	0 5	112	1 ?00	34	1 36	240	5 ?00	330	9
W T	[illegible]	100/6?	25	1 ?	34	0 3	1?4	800	18	1 00	?00	6,900	210	7
W G	88	88/65	24	? 9	16	0 4	183	600	15	1 00	380	11 000	?00	12
G D	??	1?9/73	7	2 9	46	0.8	159	1 300	37	1 45	530	11 000	?80	15
Mean	6	109/73	15	2 6	35	0 6	104	1 100	30	1 39	390	8 300	490	11
± S D	3	5/?	2	0 1	3	0.05	11	100	3	0 1	40	700	50	1
Probability	NS	< 0 05/ NS	NS	< 0 0?	†	†	†	< 0 0?	< 0 02	NS	< 0 001	< 0 001	< 0 001	< 0 001

Probabil ies (u paired t test) refer to omparison with omparabl h modynami data listed in Table I
†The means of E. [illegible] V_{cf} a d LVEDI d ffered s gn fi antly in patients with norm l and abnormal performance but patients w re grouped on the basis of these indices.

the rate of change of power a close correlation was observed between these two indices (r = 0 95) (Fig 6)

Discussion

During the i ovolumic portion of systole pres sure [illegible] related to tension along the ventricular wall as shown by the Laplace equation There fore isovolumic indices which measure combina tions of ventricular pressure and its deriva tive[4 5 1] have the advantage of reflecting tension along the ventricular wall [illegible] an uncomplicated fashion Such indices therefore may be advanta geous for assessing the function of cardiac muscle For purposes of assessing the function of the pump however it would seem appropriate to evaluate ventricular performance during ejection Several important indices of performance during

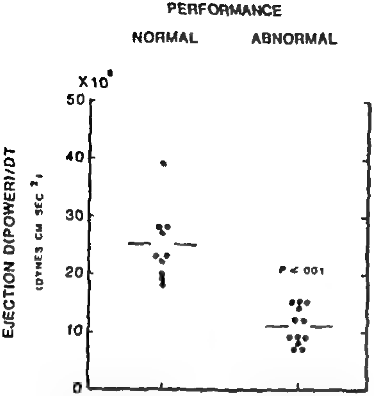


Fig 3 Individual values of the rate of change of power [d(power)/dt] measured during ejection in patients with normal performance and patients with abnormal performance

abnormal performance Strictly speaking Vmax would be theoretically invalid in these patients

Following the measurement of aortic velocity and intraventricular pressure a ventriculogram was performed as previously described[7] from which left ventricular volumes were calculated by the single plane area length method[7] The ejection fraction was calculated from the ventriculograms as the ratio of the volume ejected to end diastolic volume[8] The mean velocity of circumferential fiber shortening (V_{cf}) was measured along the minor axis of the ventricle as described by Karliner and associates[9]

Patients were categorized as having normal ventricular performance if they had an ejection fraction greater than 58 per cent,[8] a mean velocity of circumferential fiber shortening[9] greater than 1.3 sec^{-1} and a left ventricular end diastolic volume index[8] of less than 90 cm^3/m^2 There were 10 such patients Patients were categorized as having abnormal ventricular performance if their ejection fraction was less than 50 per cent[7] and their mean velocity of circumferential fiber shortening[7] was less than 1.0 sec^{-1} There were 12 such patients Patients in whom the ejection fraction was normal and the mean velocity of circumferential fiber shortening was abnormal or vice versa were excluded from the study because one could not categorize their performance with certainty It is emphasized that these groups were selected to ensure that the ventricular performance of these patients was definitely either normal or abnormal A strict classification is required in order to examine the validity of this new hemodynamic index of performance and to compare it to previously derived indices

Results

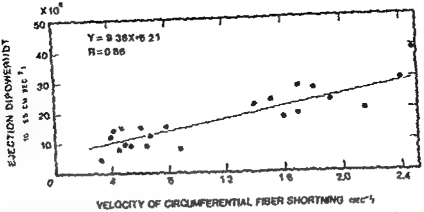
Typical curves illustrative of the relation with respect to time of aortic flow, rate of change of flow, power, and the rate of change of power are shown (Fig 2) The rate of change of power reaches a peak during the early portion of ejection and well before peak power The rate of change of power reaches peak within a few milliseconds of the peak rate of change of flow

In patients with normal performance (characterized by a normal ejection fraction and velocity of circumferential fiber shortening in the presence of a normal end diastolic volume index) the ejection rate of change of power was $(25 \pm 2) \times 10^8$ dyne cm sec^{-3} (mean ± S E) In patients with a low ejection fraction and low velocity of circumferential fiber shortening the ejection rate of change of power was $(11 \pm 1) \times 10^8$ dyne cm sec^{-3} ($P < 0.001$)* (Tables I and II) There was no overlap of values (Fig 3) In patients with normal ventricular performance the peak rate of change of power ranged between 18 and 39 × 10^8 dyne cm sec^{-3} It did not exceed 15 × 10^8 dyne cm sec^{-3} in patients with poor ventricular performance

Peak power during ejection peak flow and the peak rate of change of flow also showed a significant difference of the mean The peak flow and the peak rate of change of flow showed some overlap of values The commonly measured isovolumic indices (peak dp/dt maximum $\frac{dp/dt}{p}$ and Vmax) showed more overlap (Tables I and II)

The peak ejection rate of change of power correlated well with the mean velocity of circumferential fiber shortening (r = 0.86) (r = correlation coefficient) (Fig 4) It also correlated but less closely, with the ejection fraction (r = 0.71) (Fig 5) As would be predicted from the fact that the rate of change of flow is a component term in

* Unpaired t test



F g 4 Rate of change of pov er [d(power)/dt] m asured during ejection shown in relation to the mean velocity of circumferential fiber sh rtening Correlation coefficient (r) is shown

Table II Patients with abnormal performance (E F 50 per cent V_{cf} 1 0 sec ⁻¹)

Patient	Heart rate (b p m)	Blood pressure (mm Hg)	LVEDP (mm Hg)	Cardiac index (L / min / M²)	Ejection fraction (%)	V_{cf} (sec⁻¹)	LVEDI (cm³/M²)	Peak dp/dt (mm Hg/sec)	Peak (dp/dt)/(p) (sec⁻¹)	V_{max} (sec⁻¹)	Peak flow (cm³/sec)	Peak dQ/dt (cm³/sec²)	Peak power ×10⁴ (dynes cm./sec)	Peak d(power)/dt ×10⁶ (dynes cm/sec²)
R G	[illegible]	104/71	13	2 2	27	0 4	64	1,_00	35	1 57	3?0	7 000	400	8
B L	83	9?/65	_0	2 1	27	0 6	5?	1,500	_8	1 62	280	6 500	400	9
R. L	3	110/_0	10	2 4	48	0.9	108	1 100	30	1 _0	290	5 100	380	7
W H	80	115/8?	16	2.4	?1	0 6	87	1,200	25	1 36	400	11 000	500	15
R W	6	10_/_4	12	3 0	3_	0 ?	108	900	21	1 03	600	9 000	6_0	12
R. Y	64	90/63	14	2 2	44	0 6	74	800	2_	1 12	3_0	8,200	390	9
O B	60	100/_0	8	2 7	49	0 4	8_	900	31	1 4?	5 0	10 000	680	14
L. L B	9?	135/87	15	_	??	0 5	91	1 500	49	2 00	490	12 000	_00	15
R. N	72	134/88	15	?6	38	0 5	112	1 700	34	1.36	240	5 700	390	9
W T	64	100/67	25	1 9	34	0.3	124	800	18	1 00	200	6,900	210	7
W G	88	88/_0	?4	2 9	18	0 4	183	600	15	1 00	380	11 000	390	12
G D	72	129/73	7	2 9	46	0 8	159	1 300	3?	1 45	530	11 000	780	15
Mean	_6	109/73	15	2 6	35	0 6	104	1 100	30	1 39	390	8 300	490	11
± SD	3	5/	_	0 1	3	0 05	11	100	3	0 1	40	_00	50	1
Probability	NS	< 0 0_/ NS	NS	< 0 05	†	†	†	< 0 05	< 0 02	NS	< 0 001	< 0 001	< 0 001	< 0 001

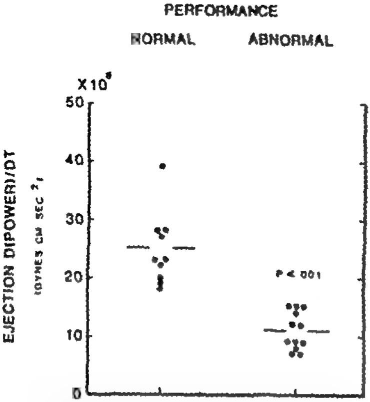
Probabil ties (npaired t test) ref r t omp rison with omp abl hemodynamic data listed in Table I

†Th m n of E F V_{cf} a d LVEDI differed signific ntly in patie s w th normal and abnormal performance but patients were grouped n the basis of these indices

the rate of change of power a close correlation was observed between these two indices (r = 0 95) (Fig 6)

Discussion

During the isovolumic portion of systole pressure is related to tension along the ventricular wall as shown by the Laplace equation There fore isovolumic indices which measure combinations of ventricular pressure and its derivative [3 11] have the advantage of reflecting tension along the ventricular wall in an uncomplicated fashion Such indices therefore may be advantageous for assessing the function of cardiac muscle For purposes of assessing the function of the pump however it would seem appropriate to evaluate ventricular performance during ejection Several important indices of performance during



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Patients were categorized as having normal ventricular performance if they had an ejection fraction greater than 58 per cent[8] a mean velocity of circumferential fiber shortening[9] greater than 1 3 sec^{-1} and a left ventricular end diastolic volume index[8] of less than 90 cm^3/m^2 There were 10 such patients Patients were categorized as having abnormal ventricular performance if their ejection fraction was less than 50 per cent[10] and their mean velocity of circumferential fiber shortening[9] was less than 1 0 sec^{-1} There were 12 such patients Patients in whom the ejection fraction was normal and the mean velocity of circumferential fiber shortening was abnormal, or vice versa were excluded from the study because one could not categorize their performance with certainty It is emphasized that these groups were selected to ensure that the ventricular performance of these patients was definitely either normal or abnormal A strict classification is required in order to examine the validity of this new hemodynamic index of performance and to compare it to previously derived indices

Results

Typical curves illustrative of the relation with respect to time of aortic flow, rate of change of flow, power, and the rate of change of power are shown (Fig 2) The rate of change of power reaches a peak during the early portion of ejection and well before peak power The rate of change of power reaches peak within a few milliseconds of the peak rate of change of flow

In patients with normal performance (characterized by a normal ejection fraction and velocity of circumferential fiber shortening in the presence of a normal end diastolic volume index) the ejection rate of change of power was (25 ± 2) × 10 dyne cm sec^{-2} (mean ± S E) In patients with a low ejection fraction and low velocity of circumferential fiber shortening, the ejection rate of change of power was (11 ± 1) × 10 dyne cm sec^{-2} ($P < 0.001$)* (Tables I and II) There was no overlap of values (Fig 3) In patients with normal ventricular performance, the peak rate of change of power ranged between 18 and 39 × 10 dyne cm sec It did not exceed 15 × 10^6 dyne cm sec^{-2} in patients with poor ventricular performance

Peak power during ejection peak flow and the peak rate of change of flow also showed a significant difference of the mean The peak flow and the peak rate of change of flow showed some overlap of values The commonly measured isovolumic indices (peak dp/dt maximum $\frac{dp/dt}{p}$ and Vmax) showed more overlap (Tables I and II)

The peak ejection rate of change of power correlated well with the mean velocity of circumferential fiber shortening (r = 0 86) (r = correlation coefficient) (Fig 4) It also correlated but less closely with the ejection fraction (r = 0 71) (Fig 5) As would be predicted from the fact that the rate of change of flow is a component term in

*Unpaired t test

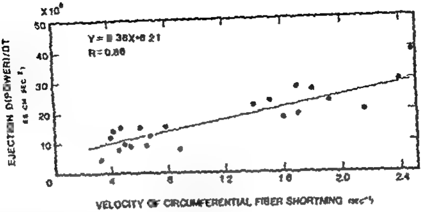

Fig 4 Rate of change of power [d(power)/dt] measured during ejection shown in relation to the mean velocity of circumferential fiber shortening Correlation coefficient (r) is shown

Table II Patients with abnormal performance (E F 50 per cent V_{cf} 1 0 sec ¹)

Patient	Heart rate (b p m)	Blood pressure (mm Hg)	LVEDP (mm Hg)	Cardiac index (L / min / M²)	Ejection fraction (%)	V (sec)	LVEDI (cm / M²)	Peak dp/dt (mm Hg/sec)	Peak (dp/dt /p) (sec)	Vmax (sec)	Peak flow (cm / sec)	Peak dQ/dt (cm / sec)	Peak power ×10⁶ (dynes cm / sec)	Peak d(power) /dt×10⁶ (dynes cm / sec)
R. G	84	104/71	13	??	?7	0 4	64	1,300	35	1 57	3?0	7 000	400	8
B L.	83	9 /65	?0	? 1	27	0 8	81	1 500	38	1 6?	2?0	6 ,00	400	9
R L.	3	110/ 0	10	2 4	46	0 9	108	1 100	30	1 ?0	290	5 100	380	7
W H	80	115/8?	1?	2 4	?1	0.6	8	1,200	2?	1.36	400	11,000	500	15
R W	76	10?/74	12	3 0	36	0	108	900	23	1 03	600	9 000	6?0	12
R. Y	[illegible]	90/63	14	? 2	44	0 8	?4	800	?5	1 12	350	8 ?00	390	9
O B	60	100/ 0	8	7	49	0 4	85	900	33	1 4?	5?0	10 000	680	14
L. L B	9?	135/87	15	3 3	?6	0 5	91	1 500	49	2 00	490	1? 000	700	1?
R. N	72	134/88	15	2 6	?8	0 5	11?	1 ?00	34	1 36	240	5 ?00	390	9
W T	64	100/?7	25	1.9	34	0 3	1?4	800	18	1 00	200	6,900	210	7
W G	88	88/6.	24	2 9	16	0 4	283	600	1?	1 00	380	11 000	390	12
G D	72	1?9/73	7	? 9	46	0 8	159	1,300	37	1 45	530	11 000	780	1?
Mean	76	109/73	15	2 6	35	0 6	104	1 100	30	1 39	390	8,?00	490	11
± S D	3	5/?	2	0 1	3	0 0?	11	100	3	0 1	40	?00	?0	1
Probability	NS	< 0 0?/ NS	NS	< 0 05	†	†	†	< 0 0?	< 0 02	NS	< 0 001	< 0 001	< 0 001	< 0 001

Probabilities (pa red t test) ref r to comparison with comparable hemodynamic data listed in Table I
†The me n of E F V and LVEDI differed s gnificantly in pat ts with normal and abnormal performance but p tients were grouped n the basis of th se indices

the rate of change of power a close correlation was observed between these two indices ($r = 0.95$) (Fig 6)

Discussion

During the isovolumic portion of systole pres sure is related to tension along the ventricular wall as shown by the Laplace equation There fore isovolumic indices which measure combina tions of ventricular pressure and its deriva tive [5] have the advantage of reflecting tension along the ventricular wall in an uncomplicated fashion Such indices therefore may be advanta geous for assessing the function of cardiac muscle For purposes of assessing the function of the pump however it would seem appropriate to evaluate ventricular performance during ejection Several important indices of performance during

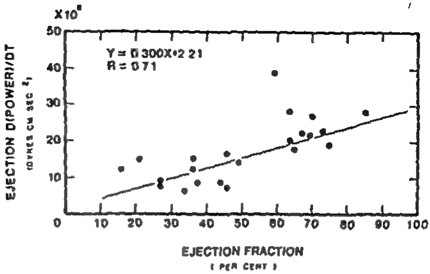

Fig. 5. Rate of change of power shown in relation to the ejection fraction.

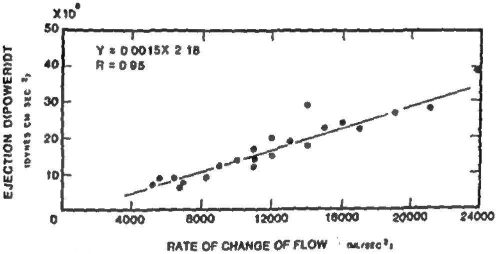

Fig. 6. Rate of change of power shown in relation to the rate of change of flow.

ejection have been utilized. These include cardiac output,[12] ventricular work,[12] ventricular power,[12] ventricular ejection rate,[13] peak flow,[14] peak rate of change of flow,[15] velocity of circumferential fiber shortening,[9] and the ejection fraction.[9] These are all useful and contribute prominently to the evaluation of the cardiac performance of patients. Even so, these indicators of cardiac function have shortcomings which warrant the continued exploration of methods for the evaluation of ventricular performance.[16]

Just as the peak rate of change of power distinguished between patients with normal and abnormal ventricular performance, peak flow, peak rate of change of flow, and peak power also distinguished between these two groups. Previous studies in dogs showed that peak flow and peak power as well as the peak rate of change of power were responsive to drug induced changes of the contractile state.[1] However, peak flow and peak power also showed significant changes with preload which were not shown with the peak rate of change of power. Studies in dogs showed that the peak rate of change of flow was the only ejection index in addition to the peak rate of change of power, which responded to drug induced changes of the contractile state and failed to respond significantly to changes of the preload and afterload.[1] The peak rate of change of power, however, although more complex in its measurement than the peak rate of change of flow, has advantages which recommend its utilization. These are its fluid dynamic basis, its physiological meaning, and its integrative characteristics. The rate of change of power indicates an acceleration of change of power indicates an acceleration of energy expended upon the production of useful work by the ventricle during ejection. Since fluid dynamic systems are comprehensively described

on the basis of considerations of the energy of the system it is likely that this acceleration of energy expenditure might be a useful expression

An advantageous feature of the rate of change of ventricular power is the encompassing character of the expression It implies information related to ventricular work ventricular power ventricular pressure aortic flow the rate of change of ventricular pressure and the rate of change of aortic flow Both ventricular power and ventricular work can be derived from the expression by integration Ventricular pressure aortic flow and their respective rates of change are components of the expression Each of these expressions has been utilized previously for the evaluation of ventricular performance [1,12,14,15] although dp/dt is best applied to the isovolumic period

It was previously shown that the rate of change of power can be written in terms of the length tension and velocity of muscle shortening [3] This is possible because tension is related to pressure by the Laplace equation and circumferential fiber length and the velocity of fiber shortening are related to flow The exact relation depends upon the shape of the ventricle The rate of change of power written in terms of tension length and velocity of shortening in the particular case of an assumed spherically shaped ventricle is

$$\text{Rate of change of power} = 8\pi\left[rT\frac{d^2r}{dt^2} + r\frac{dr}{dt}\frac{dT}{dt} + T\left(\frac{dr}{dt}\right)^2 \right] \qquad (2)$$

where T = tension along the ventricular wall (dynes/cm) r = radius (cm) dr/dt = rate of shortening of the radius (cm /sec) and d^2r/dt^2 = acceleration of shortening of the radius (cm /sec)

The relation of the ejection rate of change of power to tension length and velocity of shortening of the ventricular wall is of interest because these parameters are said to describe the contractile state of cardiac muscle preparations [7] These mechanical concepts have also been applied to the intact heart and found to be useful [8,9]

The interrelation of the rate of change of power and the velocity of shortening of the radius (and consequently circumference) shown in Equation 2 explains the close correlation observed between the rate of change of power and the velocity of circumferential fiber shortening (Fig 4)

The rate of change of power is an expression of physiological meaning that can also be applied to the isovolumic period [3,4] Its form and derivation differ from the ejection rate of change of power since no flow occurs during the isovolumic period However, the concept of an acceleration of energy expenditure has meaning during both the isovolumic phase of systole and the ejection phase and a useful evaluation of ventricular performance in patients has also resulted from the former [4]

The utility of the ejection rate of change of power in the presence of valvular disease has not yet been studied This index seemingly would be valid in the presence of mitral valvular disease and aortic regurgitation Stenosis of the aortic valve would produce a nonuniform profile of velocity across the aortic valve which might produce uninterpretable results

It may be advantageous to present the rate of change of ventricular power in a relatively nondimensional fashion This can be accomplished by normalizing it to instantaneous power The ratio of the instantaneous rate of change of power to instantaneous power we have termed the fractional rate of change of power [3] This has particular advantages since this form of the equation is such that changes of the cross sectional area of the aorta can be neglected and aortic velocity can be utilized directly in the calculations The form of the expression permits a simple relation to be shown between the velocity of circumferential fiber shortening velocity of elongation of the series elastic power flow and their rates of change providing that some assumptions are made

Summary

An expression indicative of the rate of change of ventricular power was derived and applied to the evaluation of left ventricular performance of patients with angina Patients were categorized as having normal or abnormal ventricular performance on the basis of the ejection fraction mean velocity of circumferential fiber shortening and left ventricular end diastolic volume index. In those with normal performance the ejection rate of change of power was $(25 \pm 2) \times 10$ dyne cm.sec in patients with abnormal performance it was $(11 \pm 1) \times 10^{6}$ dyne cm.sec (P < 0 001) There was no overlap of values between categories of patients Such a clear distinction between categories was not seen with any of the commonly

utilized isovolumic indices of performance The rate of change of ventricular power measured during ejection is free of assumptions, yet has a fluid dynamic as well as a physiological meaning It serves in an integrative fashion by incorporating terms previously shown to be of functional significance Previous studies in dogs showed that it reflected alterations of the inotropic state, yet it was relatively independent of alterations of preload or afterload It appears therefore that it is an indicator of ventricular performance that has desirable characteristics

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Atrial T (Ta) loop in dogs with or without atrial injury

Hiroshi Hayashi, M.D.*
Mitsuharu Okajima, M.D.**
Kazuo Yamada, M.D.***
Nagoya, Japan

In clinical electrocardiography the P wave is routinely analyzed and recognition of waveform abnormalities may be useful diagnostically. A number of studies of the P loop[1-3] have been reported and by using the electrical dissection method of the loop[4] or by the magnified recording method[5] the P loop has been investigated in detail.

Atrial repolarization has not received as much attention clinically or experimentally and little is known about the Ta loop in normal or abnormal states.

In the study described here, complete A-V block was produced in laboratory dogs and the Ta loops investigated using recordings of high amplification.

This study provides some experimental basis for better understanding of how abnormal states can change the Ta loop. This would be a preliminary for understanding the abnormalities in the human atria as well.[6]

Methods

Experiments were performed on 46 adult dogs which ranged in weight from 11 to 16 kilograms. They were anesthetized with sodium pentobarbital (Nembutal) 25 mg. per kilogram of body weight administered intravenously. The chest was opened under artificial respiration. Complete A-V block was produced by inserting a needle through the posterior wall of the right ventricle into the region of the His bundle. The P and the Ta waves of the scalar electrocardiogram (ECG) in the dogs with complete A-V block were recorded with the McFee lead system modified for canine use.[11] Left, inferior, and anterior directions of X, Y, and Z axes, respectively, were regarded as positive.

The ECG was recorded after the chest was closed. A biophysical ME amplifier BE-AII (Yokogawa Electric Co., Ltd.) and an EMO-62 six channel photorecorder (cycle specificity 0-1000 Hz, Yokogawa Electric Co., Ltd.) were used for amplification and recording. A high cut filter of 100 Hz was used in these amplifiers.

The scalar ECG's were taken simultaneously at a sensitivity of 3 cm. per 100 μV and at a paper speed of 10 cm. per second. The P and the Ta loops were constructed by hand by plotting the successive instantaneous amplitudes of each of the P and the Ta waves in the three scalar leads at 0.01 second intervals.

In the frontal and horizontal planes, 0° is set at the left extremity of the X axis and the angles inscribed clockwise are positive from 0° to +180° and those inscribed counterclockwise are negative from 0° to −180°. In the left sagittal plane 0° is set at the posterior extremity of the Z axis and angles inscribed clockwise are positive from 0° to +180° and those inscribed counterclockwise are negative from 0° to −180°. The P-Ta angle was measured from the maximum P vector to the maximum Ta vector in a clockwise direction.

In order to obtain the atrial gradient, the areas of the P and the Ta waves in the scalar ECG's were measured in the following way. The baseline connecting the beginning of the P wave and the

From the Circulation and Respiration Division, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan.

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Reprint requests: Hiroshi Hayashi, M.D., Emory University School of Medicine, Division of Cardiology, [redacted] Butler St. S.E., Atlanta, Ga. 30303.

*Research associate, Cardiovascular Research and Training Institute, College of Medicine, University of Utah, Salt Lake City, Utah.

**Professor of Medicine, College of Medicine, Fujita-Gakuen University, Toyoake, Japan.

***Professor, The Circulation and Respiration Division, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan.

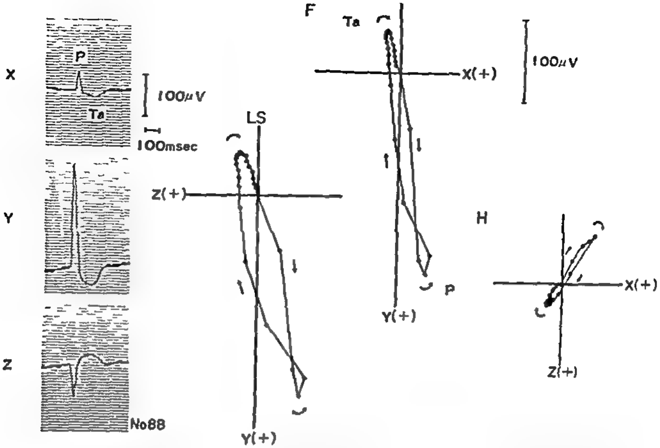


Fig 1 The P and the Ta loops without atrial injury The P and the Ta waves in Leads X Y and Z are shown on the left The graphically composed P and Ta loops are shown on the right *F* Frontal plane *H* horizontal plane *LS* left sagittal plane The P and Ta waves have opposite polarity in each lead The magnitude of the Ta wave to the P wave is fairly proportional in each lead The Ta loop is the smaller one with densely dotted portions in each of the three planes of the vectorcardiogram The loop was a long and smooth ellipse The maximum Ta vector was oriented to the right superiorly and anteriorly The direction of inscription of the Ta loop was always the same as that of the P loop—clockwise rotation — in all planes The dot indicates the time points of 10 msec interval for both the P and Ta loops This applies to all dottings on the loops in the following figures

end of the Ta wave was drawn The areas which were circumscribed by each wave and the baseline were retouched on the thick paper with equal quality and the pieces of the paper were cut out They were weighed on a direct reading microbal ance the weight being subsequently converted into the area

The algebraic sum of the P and the Ta waves in each lead was calculated These sums are the components of the atrial gradient in each scalar lead and are designated as AGx, AGy and ÂGz The spatial atrial gradient, SAG was obtained from the three components, i e ,

$$SAG = \sqrt{(AGx) + (AGy) + (AGz)}$$

In most dogs an injury of 1 to 2 cm in diameter was produced by cauterization of one of the various sites in the atria after the preinjury ECG was recorded After the production of injury, the P and the Ta loops were obtained in the same manner as has been already described

Results

Normal Ta loop An example of normal Ta loop is shown in Fig 1 The maximum Ta vector was oriented to the right superiorly and anteriorly exactly opposite to the direction of the maximum P vector

In the group of 18 dogs without atrial injury the direction of the maximum Ta vectors ranged from −104° to −140° (mean −118°) from 111° to 161° (mean 129°) and from −100° to −144° (mean −112°) in the frontal horizontal and left sagittal planes respectively (Fig 2) The magni tude of the maximum Ta vectors ranged from 39 to 64 μV (mean 56 μV) from 24 to 48 μV (mean 34 μV), and from 37 to 65 μV (mean 54 μV) in each of the three planes The direction of the maximum P

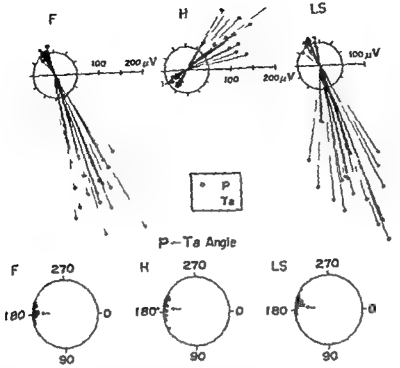


Fig 2 The distribution of the direction and the magnitude of the maximum P and Ta vectors and P Ta angle in each of the three planes being observed in the group of 10 dogs without atrial injury The maximum Ta vectors are oriented to the right superiorly and anteriorly and the maximum P vectors are directed to the left inferiorly and posteriorly The P Ta angles are close to 180 in all planes.

Table I Directions of inscription of the P and the Ta loops in the four groups of dogs with atrial injury at the different sites

	VCG								
	P loop				Ta loop				
Injury site	F	H	LS	Cases	F	H	LS	Cases	Discord rate
Rt posterior 11 cases	C	C	C	7	C	C	C	4	5 (45%)
	C	CC	C	2	C	C	CC	3	
	C	C	CC	1	C	CC	C	2	
	CC	CC	CC	1	C	CC	CC	1	
					CC	C	CC	1	
Rt. anterior 7 cases	C	C	C	5	C	C	C	6	1 (14%)
	C	C	CC	1	CC	C	C	1	
	CC	C	C	1					
Lt posterior 6 cases	CC	C	C	3	C	CC	C	3	5 (83%)
	CC	C	CC	1	C	C	CC	1	
	C	CC	C	1	CC	CC	CC	1	
	C	C	C	1	C	C	C	1	
Lt anterior 6 cases	CC	C	CC	4	CC	C	C	4	3 (50%)
	CC	C	C	2	CC	C	CC	1	
					C	CC	CC	1	

*The numbers and percentages of the cases in which the direction of inscription of the P and the Ta loops is not exactly the same in each of the three planes.
C, Clockwise rotation CC, counterclockwise rotation F frontal plane H horizontal plan LS left sagittal plane

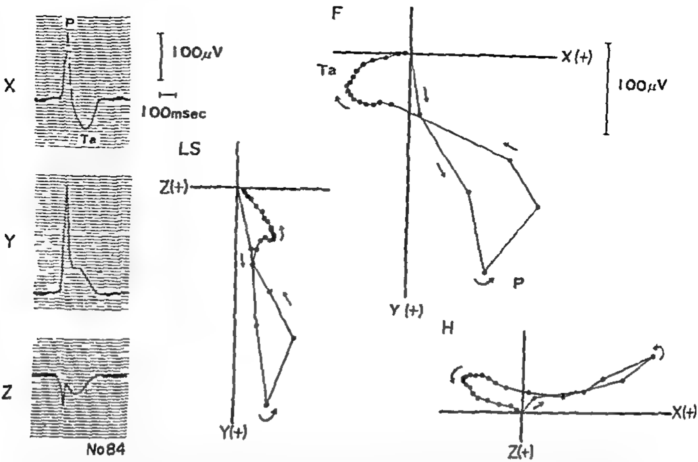


Fig 3 The P and the Ta loops with injury of the posterior wall of the right atrium The Ta wave is very large in Lead X and it deviates completely to the same direction as the P wave in Leads Y and Z The Ta loop is notched and relatively large compared to the P loop in each plane and it is displaced to the right inferiorly and posteriorly The P Ta angle is markedly small in the frontal and left sagittal planes The direction of inscription of the Ta loop is counterclockwise in both horizontal and left sagittal planes

vectors was to the left inferior and posterior Their magnitudes ranged from 75 to 406 μV

The ratio of the magnitude of the maximum Ta vector to that of the maximum P vector (Ta/P) was 0 20 0 28 and 0 19 in each of three planes on the average The mean value of the P Ta angle was 183° 188°, and 187° in each of the three planes The direction of the spatial atrial gradient was to the left, inferior and anterior (Fig 11) Its magnitude ranged from 1 4 to 5 1 μVsec with a mean of 3 1 μVsec

Ta loop after injury of the posterior wall of the right atrium *A typical atrial vectorcardiogram* with injury in this region is shown in Fig 3 The direction and the configuration of the Ta loop changed markedly

In the group of 11 dogs with injury in this region, the direction of the maximum Ta vectors was to the right, inferior and mostly anterior (Fig 4) The magnitude of the vectors ranged from 20 to 145 μV from 17 to 112 μV, and from 22 to 130 μV in each of the three planes The maximum P vectors were directed to the left, inferiorly and posteriorly in most dogs and their magnitudes were from 60 to 287 μV The Ta/P ratio of the maximum vectors ranged from 0 07 to 1 27 in the three planes The P Ta angle ranged from 27° to 143° (mean 85°) from 140° to 232° (mean 176°) and from 334° to 87° (mean 29°) in each of the three planes (Fig 5)

As shown in Table I the Ta loops showed clockwise rotation in each of the three planes in four out of 11 dogs (36 per cent) The remaining seven dogs exhibited counterclockwise rotation in at least one plane of the three In five of 11 dogs (45 per cent) the direction of inscription of the P and the Ta loops did not coincide completely in each of the three planes

An example of the spatial atrial gradient among the 11 dogs in this group is shown in Fig 11 SAG was oriented to the right inferiorly and posteriorly, and its magnitude ranged from 5 4 to 22 0 μVsec with a mean of 10 2 μVsec

Ta loop after injury of the anterior wall of the

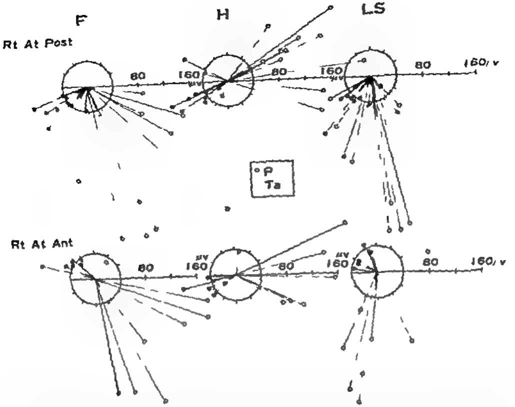


Fig 4 The distribution of the maximum P and Ta vectors in the group of dogs with injury at the right atrium In all 11 dogs with injury of the posterior wall (top) the maximum Ta vectors are directed to the right and inferiorly In all seven dogs with injury of the anterior wall (bottom) the maximum Ta vectors are oriented to the right superiorly and anteriorly

right atrium An example of the atrial vectorcardiogram is shown in Fig 6 The right component of the Ta loop increased slightly

In the group of seven dogs with injury in this region the direction of the maximum Ta vectors was to the right superior and anterior in all cases (Fig 4) The magnitude ranged from 32 to 88 μV from 23 to 85 μV and from 29 to 45 μV in each of the three planes The maximum P vectors were oriented to the left and inferiorly They were oriented anteriorly in four dogs Their magnitude was from 38 to 220 μV The Ta/P ratio of the maximum vectors ranged from 0 16 to 1 26 in the three planes

The P Ta angle ranged from 146 to 204° (mean 175) from 109° to 219 (mean 162) and from 93 to 183 (mean 126) in each of the three planes (Fig. 5)

One out of seven showed counterclockwise rotation of the Ta loop in the frontal plane (Table 1) Direction of inscription in the others was the same as in the preinjury stage SÂG was directed

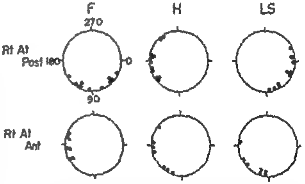


Fig 5 The distribution of the P Ta angles in the group of dogs with injury of the posterior wall (top) and the anterior wall (bottom) of the right atrium.

rightward superiorly and anteriorly in all dogs (Fig 11) and its magnitude ranged from 1 9 to 8 6 μVsec with a mean of 4 0 μVsec

Ta loop after injury of the posterior wall of the left atrium An example of the atrial vectorcardiogram is shown in Fig 7 The direction and the configuration of the Ta loop changed markedly

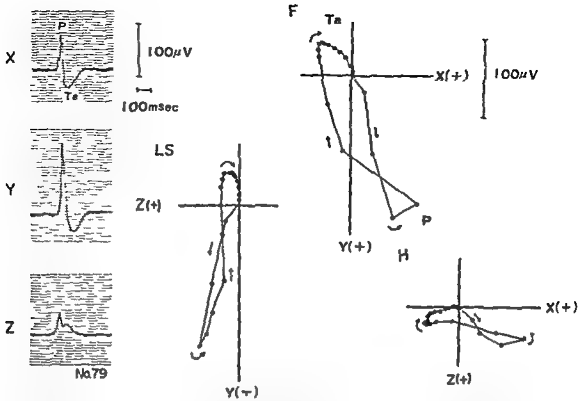


Fig 6 The P and the Ta loops with injury of the anterior wall of the right atrium The Ta wave is large in Lead X There is no negative component of the P wave in Lead Z showing a positive P wave an Ra (atrial R) wave The Ta loop is notched and is relatively large compared to the P loop in the horizontal plane The maximum Ta vector is oriented to the right superiorly and anteriorly Its direction of inscription is clockwise in all planes

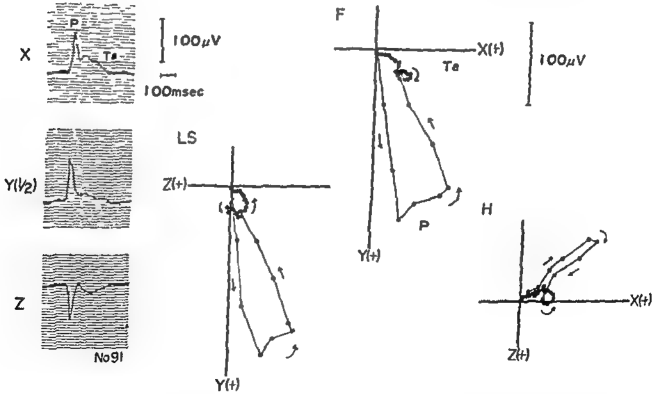


Fig 7 The P and the Ta loops with injury of the posterior wall of the left atrium The Ta wave deviates completely to the same direction as the P wave in every lead positive in Leads X and Y negative in Lead Z The Ta waves are not smooth in all leads The Ta loop is very irregular in shape and described in the same quadrant as the P loop—the left inferior and posterior quadrant The maximum Ta vector is oriented to the left inferiorly and posteriorly The P Ta angle is very small in all planes

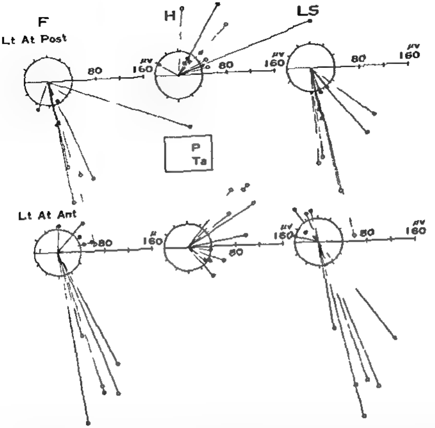


Fig 8 The distribution of the maximum P and Ta vectors in the group of dogs with injury at the left atrium In five out of six dogs with injury of the posterior wall (top) the maximum Ta vectors are directed to the left inferiorly and posteriorly In all six dogs with injury of the anterior wall (bottom) the maximum Ta vectors are oriented to the left superiorly and anteriorly

In five of six dogs with injury in this region the maximum Ta vectors were directed leftward inferiorly and posteriorly (Fig 8) The magnitude ranged from 37 to 73 μV from 23 to 51 μV and from 39 to 88 μV in each of the three planes The direction of maximum P vectors was to the left inferior and posterior Their magnitude was from 50 to 288 μV The Ta/P ratio of the maximum vectors ranged from 0 13 to 0 74 in the three planes The P Ta angle ranged from 319 to 43° (mean 5°) from 224° to 31° (mean 333°) and from 345 to 12 (mean 355) in each of the three planes (Fig 9) Five of six dogs (83 per cent) had counterclockwise rotation of the Ta loop in any one of the three planes (Table I) In five of six cases or 83 per cent the direction of inscription of the P and the Ta loops did not agree completely in each of the three planes SAG was oriented to the left inferiorly and posteriorly (Fig 12) and its magnitude ranged from 6 5 to 15 2 μVsec with a mean of 10 0 μVsec

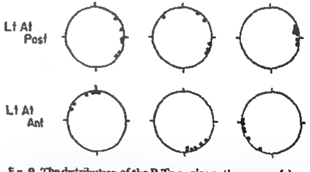
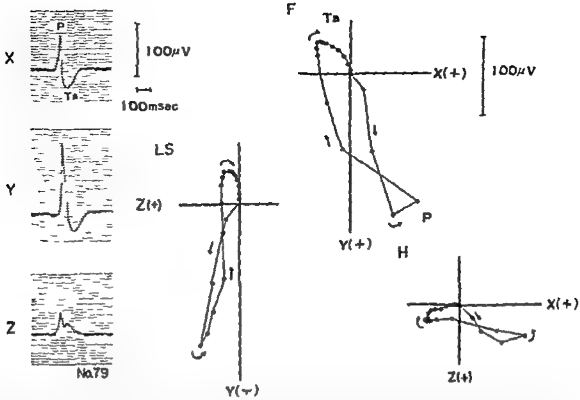


Fig 9 The distribution of the P Ta angles in the group of dogs with injury of the posterior wall (top) and the anterior wall (bottom) of the left atrium

Ta loop after injury of the anterior wall of the left atrium An example of the atrial vectorcardiogram is shown in Fig 10 The Ta loop is small compared to the P loop and the direction of the inscription of the Ta loop changed

In the group of six dogs with injury in this region the maximum Ta vectors were directed to



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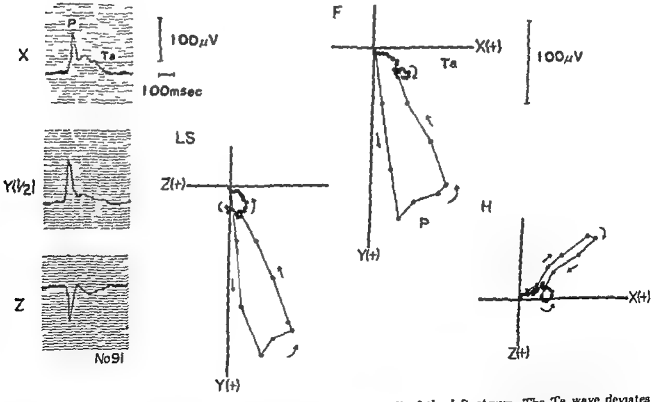

Fig 7 The P and the Ta loops with injury of the posterior wall of the left atrium The Ta wave deviates completely to the same direction as the P wave in every lead positive in Leads X and Y negative in Lead Z The Ta waves are not smooth in all leads The Ta loop is very irregular in shape and described in the same quadrant as the P loop—the left inferior and posterior quadrant The maximum Ta vector is oriented to the left inferiorly and posteriorly The P Ta angle is very small in all planes

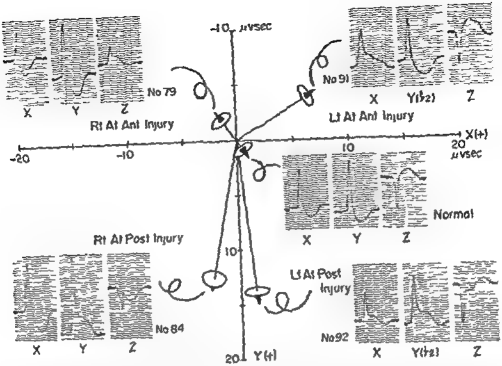

Fig 11 An example of the spatial atrial gradient (SAG) for each group of dogs without injury and with injury at the four different sites of the atria The normal SAG is very small and is oriented to the left inferiorly and anteriorly In the cases with injury the gradient is very large and is directed to the site of injury viewed from the center of both atria

cannot be observed in clinical practice except when A V block exists we can recognize various abnormalities in the atria by noting even the initial portion of the Ta loop as it is susceptible to *abnormal conditions* particularly in its initial portion In this study Ta loops observed before the production of injury to the atria were regarded as normal Ta loops That is complete A V block achieved experimentally in the initial stage was considered not to have affected the P and the Ta loops pattern appreciably

Even though the chest was closed when the atrial complex was recorded it was obvious that the volume conductor was altered appreciably due to the pneumothorax and/or atelectasis However the P waves in the scalar leads did not seem to be greatly different in amplitude shape and polarity before and after opening the chest as is the case with the ventricular complex This fact might be attributed to the anatomic and/or physiologic characteristics of the atria

The exactly opposite direction of the maximum Ta vector to that of the maximum P vector in normal dogs implies that the order of atrial repolarization is likely to follow that of depolarization If that is the case it is not unexpected that the P and the Ta loops exhibited the same direction of inscription in all planes

The P loop made a transition to the Ta loop without being closed This can be explained by the findings that the duration of the membrane action potential is short the plateau is not usually observed in atrial muscle fibers and the recovery process of atrial excitation starts before the propagation process is completed In other words there is no stage when the entire atria are in the depolarization phase as is the case with the ventricles

An alternative explanation might be that there is injury current in the atria due to the acute procedure The initial portion of the Ta wave in the scalar leads—the transitional portion of the P and the Ta waves—had amplitude and shape which remained nearly the same both before and after the production of A V block So the injury current does not seem to play a major role in this event

In the present study the atrium was cauterized

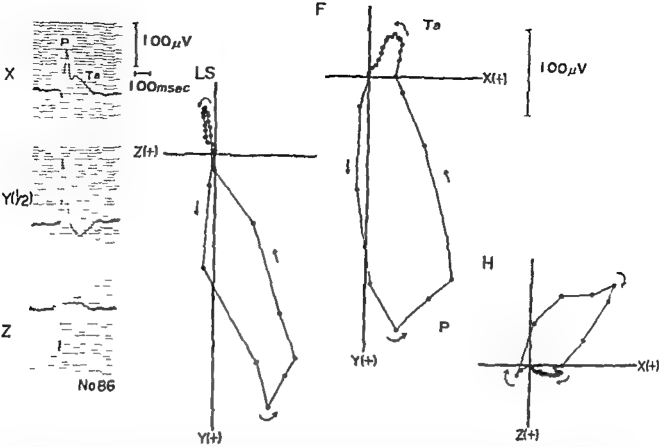

Fig 10 The P and the Ta loops with injury of the anterior wall of the left atrium The Ta wave is recorded in the same direction as the P wave in Lead X The P wave is preceded by a small negative (Qa—atrial Q wave) and a small positive deflection (Ra atrial R wave) in Leads Y and Z respectively The Ta loop is notched and relatively small as compared to the P loop in each plane The maximum Ta vector is oriented to the left superiorly and anteriorly The direction of inscription of the Ta loop is counterclockwise in the frontal and left sagittal planes The P Ta angle is small in the horizontal plane

the left superiorly and anteriorly, in all six (Fig 8) The magnitude ranged from 45 to 62 μV from 38 to 65 μV, and from 28 to 65 μV in each of the three planes The maximum P vectors were oriented leftward, inferiorly and posteriorly Their magnitude ranged from 87 to 302 μV The Ta/P ratio of the maximum vectors ranged from 0 11 to 0 47 in the three planes The P Ta angle ranged from 200° to 274° (mean 244°), from 45° to 83° (mean 67°) and from 111° to 181° (mean 158°) in each of the three planes (Fig 9) All six dogs showed counterclockwise rotation of the Ta loop in any one of the three planes as shown in *Table I In three of six dogs (50 per cent) the* direction of inscription of the P and the Ta loops did not agree completely in each of the three planes SAG was oriented leftward, superiorly and anteriorly (Fig 11), and its magnitude ranged from 6 5 to 10 7 μVsec with a mean of 8 6 μVsec

Discussion

The Ta loop has not been extensively studied because it is very small in size and merges with the QRS loop for the most part Only in the case of A V block does it emerge independently from the QRS loop In common practice the junctional portion between the P and the QRS loops is identified as a part of the Ta loop[ ] Brody and associates[14] investigated the Ta vector in human patients using computer aided signal averaging However, the complete contour of the Ta loop has not yet been reported

Previously we reported data on the Ta loop of dogs with experimentally produced A V block[13] and the Ta loop of clinical cases with A V block[15,16] We now report more concerning the normal Ta loop in dogs as well as new data concerning Ta loop in dogs with experimentally induced localized atrial lesions

Although the complete figure of the Ta loop

relative magnitude of the maximum Ta vector to that of the maximum P vector changed markedly.

The change of the P loop remained minimum. The maximum Ta vector and spatial atrial gradient were oriented toward the atrial injury site. The magnitude of the spatial atrial gradient was extremely large after injury. These findings were thought to be important in suggesting the presence of atrial injury and its localization.

The authors wish to express their appreciation to Dr. K. Millar for her constructive comments, criticisms, and valuable help in English.

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to make a localized atrial lesion It may be safer to regard the lesion as an injury rather than a complete destruction of the myocardium Hence the term "injury was used in this report rather than atrial infarction By way of confirming this reasoning, the changes in the P loop due to cauterization were small compared to those of the Ta loop, both immediately after the procedure and in the period up to 6 to 8 hours after cauterization

After making the atrial injury, the direction of the maximum Ta vectors changed markedly and systematically, according to the sites of the injury Also the Ta loops became irregular in shape The Ta/P ratios of the magnitude of the maximum vectors changed markedly with the P Ta angles becoming very small Thus the Ta loop changed markedly without accompanying the appreciable changes in the P loop and the close relationship between the two loops disappeared after the injury

The specific changes of the Ta loop due to the different sites of atrial injury showed predictive value in localizing the sites of atrial injury That is the maximum Ta vector was oriented to the right and inferiorly after right posterior injury and to the right, superiorly and anteriorly after right anterior injury It was directed leftward inferiorly and posteriorly, after left posterior injury in most cases and to the left, superiorly and anteriorly, after left anterior injury In this manner the maximum Ta vector pointed toward the site of atrial injury

The P Ta angle became markedly distorted from the normal value of 180° after injury at any of the sites This angle in each plane varied according to the site of atrial injury

As described above, the maximum Ta vector was directed toward the site of atrial injury and the maximum P vector was mostly unchanged Therefore the P Ta angle in each plane can easily be presumed for any site of atrial injury

Occasionally the direction of inscription of the Ta loop was also a useful aid in finding atrial abnormalities The counterclockwise rotation of either the P or Ta loop and/or the discordance in the direction of inscription between these two loops was thought to be an important finding to suggest abnormalities of atrial muscle, especially so when the left atrium was involved

The direction of the area vector i e atrial gradient, which was obtained from the scalar ECG s, pointed to the atrial injury site out from the center of the atria as did the maximum Ta vector According to the concept of the ventricular gradient of Wilson and associates,[17] the gradient is directed from the area where the duration of excitation is longer toward the area where it is shorter If the injury produced mimics that due to ischemia, the duration of action potential will become short at the injured area during the acute stage with the duration of excitation being shorter than that of the intact area and the atrial gradient will point toward the injured area

As the direction of spatial atrial gradient served nearly the same diagnostic value as that of the maximum Ta vector in determining the injury site in the atria, it seemed that spatial atrial gradient was less valuable in this study especially considering the difficulty in obtaining it However there seems to be some possibility that the magnitude of the spatial atrial gradient might have some relationship to the severity or size of the injury, or to the stage of the injury Further elaboration on this matter is to be desired The accuracy of the method used in this study to measure the P and the Ta waves was fairly high In our preliminary study the reproducibility of the paper weight and the conversion from the weight to the area were satisfactory

Summary

In 46 dogs with experimentally produced complete A V block, the P and the Ta waves before and after the atrial injury were recorded in scalar orthogonal ECG leads at high speed and high amplification The P and the Ta loops were drawn by hand from the scalar ECG s In the dogs without atrial injury the maximum Ta vector was oriented to the right, superiorly and anteriorly The P Ta angle was close to 180° in each of the three planes The magnitude of the maximum Ta vector was nearly proportionate to that of the maximum P vector in each plane The Ta loop was a smooth elongated ellipse in configuration and showed clockwise rotation in all planes, as did the P loop The spatial atrial gradient obtained from the scalar ECG was small

In the dogs with atrial injury, the Ta loop changed in the direction, configuration, and inscription direction The P Ta angle and the

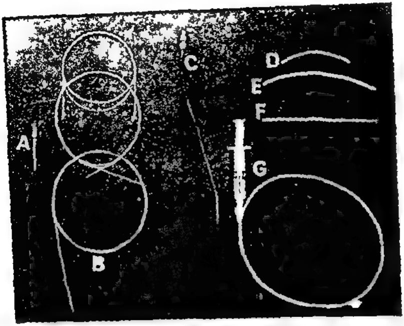

Fig 1 Equipment used for PBAS A thin walled needle B representative steel guide wires C woven Teflon catheter D Teflon dilator E larger Teflon dilator through mylar sheath (F) and G partially inflated No 5 dilation catheter

spite initial attempt at percutaneous insertion

Patients excluded from the study were those with single ventricle tricuspid atresia or "corrected transposition those initially catheterized beyond 3 months of age and the few infants ballooned in 1966 when septostomy was a newly described technique All procedures were performed by the authors or senior cardiology trainees under direct supervision of the authors When the sample was significantly large biostatistical analysis (Student's t test) was used to compare results

Results

PBAS PBAS was attempted in 30 infants and accomplished in 25 The balloon catheter could not be inserted in five in four (weight 5½ to 8¼ pounds) the vein could not be initially entered percutaneously and in the other patient (weight 6 pounds) the balloon catheter could not be inserted into the vein despite successful percutaneous diagnostic catheterization Thirteen of those treated by PBAS weighed less than 8 pounds The mean aortic oxygen saturation rose from 55 per cent before ballooning to 72 per cent ($p < 0.005$) after ballooning Twenty four patients demonstrated an early improvement in clinical status and oxygen saturation In one case the procedure was performed twice without discernible physiologic or clinical benefit This infant then underwent surgical septostomy but died following surgery Postmortem examination disclosed two atrial defects one presumably produced by the ballooning

Other complications consisted of (1) the above mentioned patient was noted at surgery to have an atrial wall perforation that had sealed itself—there were however approximately 30 c c of blood in the pericardial cavity (2) one infant had a mild infection at the percutaneous site that responded well to antibiotics (3) two patients required transfusion of 5 to 10 c c /per kilogram packed cells following the procedure However one had a precatheterization hemoglobin of only 14 0 mg. per 100 ml which exaggerated the postballooning anemia (hemoglobin 12 0 mg) and (4) one patient developed atrial flutter fibrillation which spontaneously converted 6 hours after septostomy

Twenty three PBAS patients had repeat catheterization In 17 the vein used for PBAS was again used Angiography disclosed a blocked inferior vena cava in one case and isolated femoral vein occlusion in one patient In two of the others percutaneous catheterization of the vein previously used for PBAS was unsuccessfully

Percutaneous balloon atrial septostomy in infants with transposition of the great arteries

Roger A Hurwitz, M D
Donald A Girod M D
Indianapolis Ind

Since the report of Rashkind and Miller in 1966[1] atrial septostomy has generally been the palliative treatment of choice for neonates with transposition of the great arteries (TGA) The procedure, as commonly performed by inguinal cutdown requires meticulous dissection It may necessitate ligation of the femoral vein or result in significant inguinal scarring making succeeding catheterization more difficult

Though percutaneous catheterization of infants and children has been performed in increasing numbers[5] septostomy catheters have not been introduced percutaneously Since almost all our catheterizations are performed by the percutaneous technique we endeavored to expand this approach to include balloon septostomy

It is the purpose of this paper to describe initial experience with percutaneous balloon atrial septostomy (PBAS) in palliation of infants with TGA To test effectiveness PBAS was then compared to septostomy as performed by the conventional cutdown method

Patients and Methods

Since January, 1971, PBAS has been attempted at initial catheterization of all infants with TGA admitted to the Riley Hospital for Children The PBAS procedure (Fig 1) is a modification of previously described techniques[2-4] (1) after local anesthesia the femoral vein is punctured through a thin walled 21 gauge needle (Becton Dickinson Rutherford, N J), (2) an 0 021 inch steel guide wire (Cook, Bloomington, Indiana) is advanced through the needle, (3) the site of entrance into the skin is enlarged by the tip of a No 11 scalpel blade, (4) a tapered No 4 Teflon dilator (Penntube Plastics Clifton Heights Pa) is introduced, and then withdrawn, a woven Teflon tapered No 4 catheter (Cook) is inserted for physiologic and angiographic studies After diagnosis is confirmed ballooning is performed by (1) reintroduction of the 0 021 inch wire with withdrawal of the catheter (2) progressive dilation with a tapered No 5 Teflon dilator and 0 025 inch wire and tapered No 6 Teflon dilator and 0 035 inch wire (3) insertion of a tapered No 7 or No 8 Teflon dilator covered by a snug fitting Mylar sheath (Cook) approximately 3 inches in length, (4) insertion of a No 5 dilation (septostomy) catheter (Edwards, Santa Ana, Calif) through the Mylar sheath and (5) removal of the sheath after catheter insertion Septostomy is carried out in the usual manner, using fluoroscopic frontal and lateral projection to check catheter position in the left atrium Following completion of the procedure, firm external pressure is applied approximately 1 inch cephalad to skin insertion Hemostasis is accomplished in 10 to 30 minutes

PBAS was compared to the cutdown method of septostomy as performed in our laboratory Group 1 includes those infants treated by PBAS between January 1971, and June, 1973 thus affording at least a 1 year follow up Group 2 includes all infants with TGA initially catheterized between 1967 and 1971 These underwent septostomy by routine inguinal cutdown method Group 3 includes all infants who required cutdown introduction of the septostomy catheter de

From the Department of Pediatrics Indiana University School of Medicine Indianapolis Ind

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Reprint requests R A Hurwitz M D Indiana University Hospitals Section of Pediatric Cardiology 1100 W Michigan St Indianapolis Ind 46202

but do not give exact number of minor complications or procedural time.[4] To reduce our problems with inguinal cutdown and later difficulty with insertion of catheters through scarred areas PBAS was attempted as an extension of routine diagnostic catheterization. Though of importance, size of patient has not been a limiting factor, since PBAS was performed in an infant weighing 5 pounds 5 ounces and in four others less than 7 pounds. Technically, the inability to measure pressure with a single lumen catheter is only a slight handicap. No known problems occurred due to catheter position during septostomy. In addition, atrial pressure gradients before ballooning and at repeat catheterization had only fair correlation with apparent size of the septal defect.

Though PBAS afforded initial palliation to 24 infants, five who appeared well palliated required early surgery due to inadequate atrial mixing. Two of these had anatomically adequate septal defects suggesting the severe desaturation to be caused by factors other than actual size of atrial communication. In three there was a very thick atrial septum with an inadequate defect. Perhaps this thick septal tissue allowed the foramen ovale to stretch but not tear. It might also be that the initial septostomy caused an inflammatory process with hypertrophy, scarring and later closure of the defect. The early clinical effectiveness of the percutaneous single lumen catheter septostomy is similar to that reported after femoral vein cutdown and insertion of single and double lumen catheters.[1] When we compared our own success in PBAS to the cutdown method of septostomy, early gains from percutaneous technique were less bleeding, less local infection, and slightly less procedural time. The latter was true even with addition of those requiring cutdown after unsuccessful attempted PBAS. In addition, the total percutaneous technique afforded access to an arterial line for monitoring without further deep femoral dissection and arterial repair.

It might be that if we waited for our ballooned patients to reach an older age for open repair, the septostomy created by a No. 5 catheter would not be as effective as that created by larger catheters. However, in an effort to minimize complications such as cerebral vascular accidents, we and other[1] have been performing the intra-atrial baffle operation[1] when children approach 20 pounds. Approximately 70 per cent of our patients with PBAS reached that size with no further septostomy or septectomy. This figure compares favorably with other reports[1,*,1] and our own results using various-sized catheters inserted by cutdown.

Repeat catheterization is usually necessary for patients with TGA. The percutaneous method often preserves vessels, and in 17 patients in this study repeat catheterization was performed through the vein used for PBAS. This was significantly higher than the figure achieved in those ballooned by previous cutdown. One patient from each group had a thrombosed inferior vena cava; however, this complication has been observed in other cardiac patients, especially those with cyanosis.[1] Use of umbilical veins would totally spare femoral vessels.[*] Unfortunately, more than half the patients with TGA enter the hospital beyond expected sinus venosus patency.

Summary

Initial experience with PBAS in early management of neonates with TGA is described. Standard percutaneous techniques were used and modified by a series of dilations designed to introduce a septostomy catheter into the femoral vein. Thirty infants with TGA were catheterized and PBAS was accomplished in 25. The mean aortic oxygen saturation rose from 55 to 72 per cent. Twenty-four infants were clinically palliated for at least 3 months; however, five required pre-elective surgery thought due to inadequate atrial mixing. No severe complications followed PBAS. Twenty-three patients underwent follow-up catheterization, in 17 through the vein used for PBAS. When compared to patients with TGA who had cutdown insertion of balloon septostomy catheters, the group treated by PBAS was similar in patient material and successful septostomy. Those ballooned percutaneously had fewer complications and required slightly less time for the procedure.

We feel that PBAS is a relatively easy and safe palliative procedure when performed in an infant with TGA. It should be considered by all those performing percutaneous diagnostic catheterization in infants and children.

Addendum

Since the manuscript was written, we have been able to insert No. 5 balloon catheters into a commercially available No. 7 sheath (special

Table I Infants with transposition of the great arteries catheterized from January, 1967, to June 1973*

	Group 1†		Group 2		Group 3	
	Values	No of patients	Values	No of patients	Values	No of patients
Age (days)	11	(25)	17	(28)	20	(5)
Weight (Kg)	3 6	(25)	3 5	(28)	3 7	(5)
Associated defects	10	(25)	14	(28)	1	(5)
Aortic saturation (%)	55→72	(25)	56→71	(11)	52→70	(3)
Procedure time (min)	131	(16)	144	(16)	155	(4)
Complications						
Death	0	(25)	0	(28)	0	(5)
Bleeding or infection	3	(25)	7	(29)	1	(5)
Inadequate septostomy						
Immediate	1	(25)	1	(29)	0	(5)
Later	5	(24)	6	(26)	1	(5)
Blocked inferior vena cava	1	(24)	1	(22)	0	(5)

*All weights, ages aortic saturations and times are group mean values

†Group 1 = percutaneous balloon atrial septostomy Group 2 = balloon atrial septostomy by cutdown catheter insertion Group 3 = balloon atrial septostomy by cutdown after unsuccessful attempt at percutaneous catheter insertion

attempted Angiographic study of vein patency was not done in these two patients

All 24 patients initially palliated by PBAS were living at the end of 3 months By our own criteria and those of others[1] however inadequacy of intra atrial mixing became evident before 1 year of age in five patients These patients became pro gressively more cyanotic and irritable failed to gain weight and showed increasing cardiomegaly by roentgenogram Arterial oxygen saturations were less than 55 per cent in four At surgery an unusually thick atrial septum and small defect was seen in three and large atrial septal defects were noted in two

Comparison of PBAS and cutdown technique (Table I) Twenty eight patients (Group 2) under went septostomy with catheters inserted by cutdown Twelve had septostomy with No 6 5 Rashkind catheters 10 with No 5 Edwards embo lectomy catheters, and 6 with No 5 Edwards sep tostomy catheters The mean weight and mean age of these patients were not statistically different from those in Group 1 There was how ever, a slightly greater incidence of additional cardiac defects in Group 2 The procedure resulted in a statistically similar increase in aortic oxygen saturation in both groups Catheteriza tion and septostomy by cutdown required slightly more time and had a greater incidence of minor complications of wound infection and/or bleed ing Early and late adequacy of septostomy was the same for both techniques The type and size of catheter had no apparent significance Repeat catheterization disclosed a blocked inferior vena cava in one patient from both Groups 1 and 2 In nine of 17 attempts patients were successfully recatheterized from the same leg as used for cutdown septostomy

Five patients required introduction of septost omy catheters following an unsuccessful attempt at percutaneous introduction (Group 3) The procedure time was 11 minutes longer than in those initially treated by cutdown catheter inser tion Otherwise the patients and results were similar to those in Groups 1 and 2

Discussion

Percutaneous catheterization was developed to reduce technical problems and minimize time spent with catheter insertion All catheterizations at Riley Hospital for Children are attempted percutaneously with an 80 to 90 per cent success rate in infants[1] For technical reasons of table position and vena caval anatomy the right leg is more easily used If a hematoma develops before catheter insertion or if there is a decrease in arterial pulsation we switch to the left leg When catheters are not inserted in 25 minutes, we perform an inguinal cutdown

Early reports of ballooning by saphenous cut down advise careful meticulous dissection prophylactic blood type and cross match etc

but do not give exact number of minor complications or procedural time [8] To reduce our problems with inguinal cutdown and later difficulty with insertion of catheters through scarred areas PBAS was attempted as an extension of routine diagnostic catheterization Though of importance size of patient has not been a limiting factor since PBAS was performed in an infant weighing 5 pounds 5 ounces and in four others less than 7 pounds Technically the inability to measure pressure with a single lumen catheter is only a slight handicap No known problems occurred due to catheter position during septostomy In addition atrial pressure gradients before ballooning and at repeat catheterization had only fair correlation with apparent size of the septal defect

Though PBAS afforded initial palliation to 24 infants five who appeared well palliated required early surgery due to inadequate atrial mixing Two of these had anatomically adequate septal defects suggesting the severe desaturation to be caused by factors other than actual size of atrial communication. In three there was a very thick atrial septum with an inadequate defect Perhaps this thick septal tissue allowed the foramen ovale to stretch but not tear It might also be that the initial septostomy caused an inflammatory process with hypertrophy scarring and later closure of the defect The early clinical effectiveness of the percutaneous single lumen catheter septostomy is similar to that reported after femoral vein cutdown and insertion of single and double lumen catheters [8] When we compared our own success in PBAS to the cutdown method of septostomy early gains from percutaneous technique were less bleeding less local infection and slightly less procedural time The latter was true even with addition of those requiring cutdown after unsuccessful attempted PBAS In addition the total percutaneous technique afforded access to an arterial line for monitoring without further deep femoral dissection and arterial repair

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Initial experience with PBAS in early management of neonates with TGA is described Standard percutaneous techniques were used and modified by a series of dilations designed to introduce a septostomy catheter into the femoral vein. Thirty infants with TGA were catheterized and PBAS was accomplished in 25 The mean aortic oxygen saturation rose from 65 to 72 per cent Twenty four infants were clinically palliated for at least 3 months however five required pre-elective surgery thought due to inadequate atrial mixing. No severe complications followed PBAS Twenty three patients underwent follow up catheterization in 17 through the vein used for PBAS When compared to patients with TGA who had cutdown insertion of balloon septostomy catheters, the group treated by PBAS was similar in patient material, and successful septostomy Those ballooned percutaneously had fewer complications and required slightly less time for the procedure

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Some quantitative estimates of inhomogeneity effects in electrocardiography

Stanley Rush
Albert F Baldwin
Burlington Vt

From the earliest days of electrocardiography the possible influence of thoracic tissue electrical inhomogeneities on the records has been a subject of concern Numerous difficulties hampered progress in resolving questions raised by presumed differences in the conductivities of lung myocardium blood liver etc One major problem was the uncertainty about the actual values of these conductivities One of the authors and his collaborators published an extensive study of thoracic tissue conductivities in 1963 in which independent measurements of conductivity and anisotropy were reported In addition where discrepancies were found in prior modern measurements [2,3] experiments were repeated using the same measurement techniques and those discrepancies were explained Consequently it was felt that substantial agreement had been reached and that efforts to acquire a quantitative understanding of the significance of differences in conductivities in ECG interpretation were warranted The second major problem was the practical difficulty of obtaining realistic heart lead transfer coefficients that accounted for conductivity variations Many possibilities had been proposed and utilized including cadavers [4] two dimensional models using fluid flow mappers [5] resistive papers [6] and electrolytic tanks [7] The limitations of these techniques resulted in a situation in which almost all research was being carried on with coefficients derived from three dimensional homogeneous electrolytic tank torso models The only three dimensional inhomogeneous model of which we were aware at the time work was initiated was that of Burger and van Milaan [8] who used sand bags for lungs and cork for the spine and a one third life size scale Transfer coefficients from a single point in the heart to the Burger tetrahedron were obtained with this device

In 1963 Rush initiated an effort to determine realistic heart lead transfer coefficients with the development of a new technique for constructing a detailed inhomogeneous anisotropic model of the human torso The technique was subsequently employed to reproduce the varying electrical properties of the chest in a twice-life size model of the human torso (hereafter referred to as the UVM model) The details of construction and instrumentation were published in 1971 In the interim integral equation methods were introduced by Gelernter and Swihart [9] with further theoretical developments and actual computations following rapidly thereafter The introduction of inhomogeneities to these models has been relatively limited compared to those in the UVM model because of difficulties of computation and preparation of input data and the anisotropic nature of the skeletal muscle has not yet been considered Moreover published systematic studies with these models have been restricted to rather specialized objectives distinct from those reported here

The data from the UVM model has been utilized previously in one study which was designed to determine the effects of inhomogeneities on a theoretical VCG that begins with a computer simulation of myocardial activation Despite the many uncertainties in such simulations the use of the inhomogeneous case transfer coefficients proved a significant factor in producing an approximately normal vectorcardiogram [11]

Experiments that have been carried out in the

From the Electric l Engineering Department, The University of V rmont, Burlington, Vt.

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Reprint requests Stanley Rush, Chairman, Electric l Engineering Department Th University of Vermont, Burlington, Vt. 05401

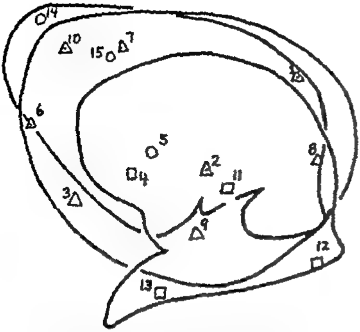

Fig 1 Three superimposed cross sections of the heart and source locations. The figure corresponds to the sections viewed from the head the sections are approximately one inch thick ' Points 12 and 13 in the atrial muscle are excluded from *the statistical calculations in Tables V VI and VII Squares* sections 25-26 triangles sections 26-27 circles sections 27 28

past by many investigators to understand effects of inhomogeneities on the ECG have been numerous and cannot be reviewed here Generally, they have resulted in qualitative conclusions which are limited due to experimental difficulties or they have utilized highly idealized models whose relationship to the real torso is questionable References to much of this work can be found in the review article by McFee and Baule[12] and in the book edited by Nelson and Geselowitz [13]

This paper presents results of two new studies which evaluate in different ways effects of body inhomogeneity and anisotropy The first is concerned with the degree to which tissue electrical properties limit the performance of vectorcardiographic lead systems In the past such lead systems were designed primarily on the basis of homogeneous, electrolytic tank experiments simply because no other techniques were available Two of these systems, the Frank[14] and the McFee Parungao[15] (or axial), have been examined here using the UVM torso in order to determine the deterioration in performance that non simple tissue properties produce The second study considers the effects of inhomogeneities and anisotropy on the problem of determining an inverse solution to constrained source generators using a least mean square error criterion This procedure for finding an inverse solution to a multiple dipole source model is currently a major focus of interest in ECG research as a result of its success in diagnosing ventricular hypertrophy [16]

Methods

The methods of analysis used in each study were simple In the case of the VCG lead study, transfer coefficients from x, y, and z unit dipoles *to the surface points corresponding to the nine* axial and seven Frank lead locations were obtained These were combined mathematically to correspond to the computations physically performed by weighting resistors In the Frank[14] *system the weightings are given in his paper* and are repeated in Eq (1)

$$
\begin{aligned}
V_x &= 610V_A + 170V_C - 781V_I \\
V_y &= 665V_F + 345V_M - 1\,000V_H \\
V_z &= 133V_A + 736V_M - 264V_I - 374V_E - 231V_C
\end{aligned} \tag{1}
$$

The x, y, z subscripts refer to the calculations of the corresponding dipole components, the sub*scripts on the right hand sides refer to the Frank* lead connection positions In the McFee Parungao system the three anterior electrode potentials and the two left side potentials are merely averaged in the sagittal and horizontal *leads leading to Eq (2)*

$$
\begin{aligned}
V_x &= (V_{L1} + V_{L2})/2 - V_R \\
V_y &= V_F - V_H \\
V_z &= V_P - (V_{A1} + V_{A2} + V_{A3})/3
\end{aligned} \tag{2}
$$

The left hand terms have the *same meaning* as in Eq (1) the subscripts F, H, P A, L and R refer to foot, head posterior, anterior, left and right locations, respectively, in the McFee Parungao system The subscript numbers refer to the two *wires of the left side connection* in the x lead and the three wires of the anterior z lead

To carry out the analyses of the axial and Frank systems tabulated data recorded from the UVM model have been used These are in the *form of potentials* at 860 body points due to a unit dipole situated in one of 15 locations in the heart and oriented in one of the three cartesian coordinate directions Each such potential represents a heart lead transfer coefficient from a dipole component at a point in the heart to a point on the body surface In effect, the Frank and McFee Parungao systems are attempts to generate inverse solutions to the net dipole components of the heart generators *To accomplish this perfectly*

Table I McFee Parungao VCG coefficients homogeneous torso

SL*	EC	X	Y	Z	α(deg)
1	x	0980	−0051	−0764	15 3
1	y	0075	0,01	−0149	18 4
1	z	003?	−015?	0,58	11 6
2	x	08,4	−0056	−0102	7 8
[illegible]	y	0036	058?	015	15 4
2	z	−0011	−0108	0753	8 2
3	x	0792	−0070	−0034	5 6
3	y	0010	0653	0019	1 9
3	z	−0109	−0123	08?1	11 3
4	x	0839	−0100	−0104	9 8
4	y	00?4	06,9	−00,1	4 9
4	z	−0039	−0159	0956	9 7
5	x	0 85	−00 9	−0064	6 3
5	y	000?	05 1	0066	8 6
5	z	−0017	−0104	0 ,7	8 0
[illegible]	x	1015	−00?2	0136	8 3
[illegible]	y	−0080	0537	0009	8 5
6	z	−0120	−0158	0856	13 1
7	x	0837	−0063	−0708	13 6
7	y	0039	060,	0030	4 6
7	z	−0003	−018	0739	13 9
[illegible]	x	103,	−00 5	−0104	6 5
8	y	0086	0,54	−0080	11 9
8	z	018,	−010?	05,5	?1 0
9	x	0 ,6	−0089	−00?,	7 0
9	y	0016	0?3?	−0064	6 0
9	z	−0010	−0122	0769	9 0
10	x	0988	−0059	−0?10	12.5
10	y	−00?5	0590	00 0	7 ?
10	z	0041	−0179	0797	13 0
11	x	0845	−0108	−0149	1?.3
11	y	00?0	0641	−0066	6 2
11	z	0085	−01,7	0?09	14 4
12	x	0 ,0	−0128	0010	9 7
1?	y	−0008	0,84	−0046	4.5
1?	z	0?04	−0089	0491	24 4
13	x	0668	−0122	0039	10.9
13	y	00?1	0704	−005?	5 0
13	z	−0086	−00?6	0834	8.8
14	x	0893	−00,9	−0875	44.5
14	y	−0079	0,66	−0293	28.2
14	z	0141	−0090	133?	7 1
15	x	0903	−0063	−0227	14 6
15	y	−0007	05 2	01,1	14 8
1,	z	0984	−0110	0 8?	10 0

*SL Source location EC excitation component

the x y and z leads must each be equally sensitive to the x y and z components respectively of the original sources regardless of the locations of the latter in the heart the component sensitivities must be equal to each other and a lead designed to measure one component must be totally insensitive to the other two The degree to which these ideal characteristics were realized in both systems was evaluated using Eqs (1) and (2) and transfer coefficients from the UVM model with and without the inhomogeneous interior

To carry out the second group of studies which are intended to evaluate the effects of inhomogeneities on a multiple dipole inverse solution a series of forward solutions from one or more dipoles was first calculated with the UVM model data In each case potentials were obtained at some 20 surface points distributed over the body The inverse solutions were then obtained (1) by conventional least mean square methods with no constraints and (2) with the *quadratic* programming method involving polarity constraints The unconstrained procedure utilized a standard computer library routine while the quadratic method follows Wolfe's[17] procedure (Both routines were extensively evaluated for accuracy with test problems) In the process of generating the forward and inverse solutions the homogeneous case coefficients were used one way and the inhomogeneous the other This procedure gives among other data a specific measure of the errors involved in obtaining realistic inverse solutions when transfer coefficients are derived from homogeneous models

Results

The results of the VCG studies are displayed in Tables I and II these refer to analyses of the axial and Frank systems respectively with the *homogeneous torso* Tables III and IV are similar but show data obtained from the inhomogeneous anisotropic torso For each source location indicated by a number in the first column of each table there is a 3 by 3 array of numbers under the columns headed X Y and Z the rows for each source location are designated x y and z to indicate source orientation The three elements in

Table II Frank VCG coefficients, homogeneous torso

SL	FC	X	Y	Z	α(deg)
1	x	0488	−0150	−0139	22 7
1	y	0052	0339	−0052	12 1
1	z	−0100	−0060	0938	7 1
2	x	0563	−0208	0156	24 8
2	y	0025	0439	0035	5 6
2	z	−0083	−0031	0539	9 3
3	x	0623	−0333	0110	29 4
3	y	0055	0553	−0074	9 5
3	z	−0014	−0031	0119	4 7
4	x	0535	−0392	0151	39 1
4	y	0090	0515	−0165	20 1
4	z	−0034	−0090	0106	13 3
5	x	0536	−0194	0195	27 2
5	y	−0011	0439	0007	1 6
5	z	−0050	−0033	0525	6 5
6	x	0620	−0233	0219	27 8
6	y	0040	0503	−0073	9 4
6	z	−0148	−0125	0368	27 8
7	x	0613	−0207	0186	40 8
7	y	0062	0471	−0203	24 3
7	z	−0077	−0120	0840	9 6
8	x	0620	−0136	0110	15 8
8	y	0079	0354	−0094	19 1
8	z	−0164	0014	0113	21 8
9	x	0579	−0265	0113	26 4
9	y	0040	0417	−0116	15 3
9	z	−0076	0027	0512	9 0
10	x	0773	−0233	0390	30 0
10	y	0047	0498	−0081	10 6
10	z	−0120	−0144	0511	20 1
11	x	0571	−0292	0142	29 5
11	y	0068	0430	−0126	18 4
11	z	−0072	−0033	0474	9 5
12	x	0618	−0207	0190	24 6
12	y	0044	0380	−0063	11 6
12	z	−0092	0047	0389	14 9
13	x	0577	−0411	0070	35 9
13	y	0055	0524	−0080	11 9
13	z	−0072	0090	0491	13 2
14	x	0943	−0160	0364	25 3
14	y	−0198	0489	0071	23 3
14	z	−0069	−0082	0338	17 5
15	x	0612	−0188	0423	37 1
15	y	−0061	0453	0201	24 8
15	z	−0021	−0076	0649	6 9

the same row as x give the strengths of the x y and z dipole components appearing in the VCG inverse solution when a unit strength dipole oriented along the x axis is used as the source which produces the surface potentials The second and third rows give similar calculations when y and z unit dipoles provide the excitation With a perfect VCG lead the diagonal terms would all be the same (the actual number is not significant here) while the off diagonal numbers would all be zero The variability in the diagonal numbers gives a measure of the degree of failure of the three (x, y z) leads to be of uniform sensitivity at a given heart location The off diagonal terms indicate the degree to which the leads lack orthogonality and parallelism to the body axes The variability of the diagonal terms from location to location in the heart is a measure of 'proximity effects (the effects of distance from the electrodes) on the lead performance

The approximate source point locations in the heart are indicated in Fig 1 The heart cross sections shown in the figure are taken from the anatomical atlas used as a guide in the construction of the model [1] The locations were chosen to give a representative sampling through the heart region but there were some practical physical restrictions on the source locations available in the model A few simple statistical measures have been calculated for the data associated with source points in the ventricular muscle region These are displayed in Table V The symbols $\bar{X}$, $\bar{Y}$, $\bar{Z}$ show the means of the corresponding diagonal x y z terms of Tables I through IV The over all mean of the diagonal terms is listed in the column labeled M The spreads of the diagonal term x y z data are indicated by the standard deviations σ_x σ_y σ_z respectively and the standard deviations as per cents of the means are given in the last three columns Tables I through IV show angles α in the last column These are polar angles measured from the x, y and z axes respectively as indicated by the row letter and have various interpretations They can be considered the magnitude of the lead field directional errors at the indicated locations in the heart or, correspondingly, the angle from an x y or z axis through which a dipole would have to be turned to give a maximum signal in the leads designed to record from that axis To calculate an α measured

Table III McFee Parungao VCG coefficients inhomogeneous torso

SL	*EC*	X	Y	Z	α(deg)
1	x	.0991	0130	−0300	18.3
1	y	0110	0808	−0252	18 8
1	z	[illegible]	−0394	1009	25 7
2	x	1074	−00[illegible]0	−0163	9 4
2	y	0072	1025	−0151	9 2
2	z	0314	−0725	0757	46 3
3	x	1090	0210	−0110	12.3
3	y	0157	0967	−0094	10 7
3	z	−0160	−0372	0948	23 2
4	x	0891	03[illegible]4	−0372	30 0
4	y	0171	1343	−0272	13 5
4	z	−01[illegible]0	−05[illegible]0	1108	26 3
5	x	1091	0047	−0169	9 1
5	y	0256	1080	0104	14.3
5	z	−0056	−0148	0896	10 0
6	x	1968	−0504	0037	11 7
6	y	−01[illegible]6	0863	0085	12 8
6	z	−0078	−.0[illegible]64	1274	12 2
7	x	1144	0032	−0546	25 6
7	y	−0030	0763	0332	23 6
7	z	−0139	−0265	1400	12 1
8	x	1461	−0440	−0257	19 2
8	y	−0791	1498	0068	27 9
8	z	−0308	0153	0645	28 1

from a particular axis the angle α_j is found as

$$\cos^{-1}(j/\sqrt{X^2 + Y^2 + Z^2})$$

where j can be X Y or Z The first column of Table VI headed α gives the mean polar angle averaged over the three sets of axes

$$\bar{\alpha} = (\alpha_x + \alpha_y + \alpha_z)/3$$

in each row The standard deviations of α α and α in degrees and in per cents of the means are also shown in the last six columns of Table VI Table VII shows the angular errors in a way which emphasizes the mean directions of the lead fields without the ambiguities of the polar angles The off diagonal x y z terms are first added algebraically component by component and a mean polar angle computed For example the terms $\widetilde{xY}$ in Table VII are the means of the terms in the Y columns and x rows in Tables I through IV the terms $\widetilde{xZ}$ are the means of terms in the Z column and x rows etc The columns headed β are the polar angles computed from the averages of the off diagonal components e g

Table III cont d

SL	*EC*	X	Y	Z	α(deg)
9	x	0745	.0106	−0212	17 6
9	y	.0063	1287	−0120	6 0
9	z	−0077	−.02[illegible]3	0023	16 0
10	x	1275	−012[illegible]	−0406	18 5
10	y	−0120	0826	0421	27.9
10	z	−0[illegible]13	−01[illegible]6	1821	8 3
11	x	0[illegible]66	0036	−0066	7 0
11	y	−0418	08[illegible]7	−0589	39.5
11	z	.010[illegible]	−03[illegible]8	090[illegible]	23.5
12	x	0729	00[illegible]9	−0134	12 1
12	y	−0153	1321	−0357	16 4
12	z	.0000	−04[illegible]5	0768	30 0
13	x	.0513	−0106	−0103	[illegible] 1
13	y	0127	1425	−0306	13 1
13	z	−0055	−.0399	1208	18 4
14	x	1442	−0[illegible]19	−1305	42.[illegible]
14	y	0142	1136	0[illegible]69	15 0
14	z	−0279	−0071	.328[illegible]	5 0
15	x	1308	0042	−06[illegible]2	27.2
15	y	.0346	1002	00[illegible]6	3 0
15	z	0004	−0090	1287	4 0

$$\beta = \cos^{-1}(\widetilde{X}/(\widetilde{X}^2 + \widetilde{xY}^2 + \widetilde{xZ}^2)^{1/2})$$

with similar definitions for β_y and β_z

When using inverse solutions to evaluate the effects of inhomogeneities, a great number of source configurations of varying complexity might reasonably be considered worthy of study A comprehensive investigation is however beyond the scope of this paper Reported here are a few calculations using simple sources in order to provide a preliminary indication of whether or not inhomogeneity effects need to be included when obtaining inverse solutions

The results of the experiments on inverse solutions are contained in Tables VIII through XII The term least refers to least mean square calculations of the inverse solution without polarity constraints on the source estimate and the term quadprog is a similar estimate with the polarities of the inverse solutions constrained to be that of the actual sources The position reference numbers in the tables indicate source locations in the heart as previously specified in the left hand columns of Tables I through IV and shown in Fig 1 The terms X_1 Y_1 Z_1 X_2 etc appearing in Tables VIII through XII indicate dipole component estimates of the inverse solution Each table shows four rows of data The first

Table IV Frank VCG coefficients inhomogeneous torso

SL	EC	X	Y	Z	α(deg)
1	x	0516	−0023	0004	2 6
1	y	0055	0554	−0211	21 5
1	z	−0020	−0247	1149	12 2
2	x	0692	−0238	0223	25 2
2	y	0081	0732	−0311	23 7
2	z	0109	−0532	0626	40 9
3	x	0774	−0160	0111	14 2
3	y	0165	0747	−0129	15 6
3	z	−0135	−0213	0491	27 3
4	x	0587	−0038	−0037	5 2
4	y	0232	0995	−0296	20 7
4	z	−0199	−0289	0492	35 5
5	x	0744	−0149	0217	19 5
5	y	0150	0782	0003	10 8
5	z	−0131	−0040	0537	14 3
6	x	1022	−0769	0346	39 5
6	y	−0000	0907	−0097	6 6
6	z	−0323	−0181	0542	34 4
7	x	0991	−0200	0303	22 1
7	y	−0011	0605	−0144	13 4
7	z	−0295	−0141	1095	16 6
8	x	0881	−0459	−0167	29 0
8	y	−0509	1129	−0250	26 7
8	z	−0391	0216	0331	52 7
9	x	0541	−0086	0035	9 7
9	y	0074	0948	−0194	12 3
9	z	−0129	−0061	0564	14 2
10	x	1094	−0371	0264	22 6
10	y	−0069	0717	−0063	7 4
10	z	−0578	−0048	0874	33 6
11	x	0496	−0130	0157	22 3
11	y	−0150	0639	−0546	41 5
11	z	−0053	−0205	0569	20 4
12	x	0593	−0085	0064	10 2
12	y	−0013	0899	−0347	21 1
12	z	−0236	−0179	0540	28 7
13	x	0406	−0297	0006	36 [illegible]
13	y	0153	1056	−0253	15 6
13	z	−0088	−0093	0720	10 1
14	x	1403	−0390	0196	17 3
14	y	−0341	0905	0375	29 3
14	z	−0853	0025	0813	46 4
15	x	0983	−0156	0252	16 8
15	y	−0069	0763	0068	7 3
15	z	−0163	−0033	0858	11 0

row displays the results obtained by using homogeneous case transfer coefficients in the forward and inverse solutions and the second row a similar use of the inhomogeneous case transfer coefficients The third row shows computations in which the forward solution (the combined surface potentials from all sources) is determined by inhomogeneous case transfer coefficients and the inverse by homogeneous case coefficients The fourth row is similar to the third except that the forward solutions use homogeneous case coefficients and the inverse solutions inhomogeneous case coefficients

Discussion

A review of the VCG Frank and axial systems results shows several interesting features In Table V the average sensitivities $\bar{X}$ $\bar{Y}$ and $\bar{Z}$ in the four *configurations studied, are shown* A measure of the deviation from equality of the three terms in each case can be defined by subtracting the smallest from the largest (the range of $\bar{X}$ $\bar{Y}$, and $\bar{Z}$) and expressing this difference as a percentage of the mean M Corresponding *to the first four rows of Table V* these are 39, 28 18, and 17 per cent respectively This shows an unexpected improvement in both systems with regard to the differences in average sensitivity in the x y z directions in the inhomogeneous as compared to the homogeneous The average sensitivity differences in the three coordinate directions in the homogeneous UVM model as compared to those in the homogeneous models from which the lead specifications were derived, probably reflects a difference in body configuration (the McFee torso model, for example, was cylindrical in shape and thus had no variation in cross section with distance in the y direction) and *in the choice of sampled points from the heart* used to compute the average lead sensitivity These results in the homogeneous torso are similar to those of Brody and Arzbaecher[19] in that the axial y lead has the least sensitivity On the other hand we did not find the high z lead sensitivity they reported and as large a spread among the *average sensitivities,* $\bar{X}$ $\bar{Y}$ $\bar{Z}$ in the three coordinate directions The Frank system in our homogeneous studies as in those of Brody and Arzbaecher showed less spread among the average sensitivities in the x y and z direction than did the

Table V Statistical parameters of VCG lead systems rectangular components

Data from	$\bar{M}$	$\bar{X}$	$\bar{Y}$	$\bar{Z}$	σ	σ	σ	%x*	%y	%z
McFee Parungao H†	0‹7	089	.059	081	009	005	.018	10	6	22
Frank H	053	061	046	053	010	006	018	16	13	34
McFee-Parungao I	115	117	104	125	033	023	068	28	22	55
Frank I	.0‹7	08?	0"9	069	027	016	025	32	21	36

% = (σ /$\bar{X}$)100 % = (σ /$\bar{Y}$)100 % = (σ /$\bar{Z}$)100
†H h mogeneous I inhom g neous.

Table VI Statistical parameters of VCG lead systems angular errors

Data from	$\bar{\alpha}$	$\bar{\alpha}$	$\bar{\alpha}$	$\bar{\alpha}$	γ	γ	γ	%x	%y	%z
McFee Parungao H	11 6	12 6	10 5	11 6	10.2	7.2	3 7	81	69	32
Frank H	18 8	28 8	15 0	12 6	6 7	7 4	7 1	23	49	56
McFee-Parungao I	18 2	19 1	17 1	18 υ	10 1	10.2	11.8	[illegible]	60	64
Frank, I	21 6	18 9	18 2	27 6	9 9	10 3	14 0	5?	57	5?

γ γ and γ are st ndard deviations of α α and α % = (γ /$\bar{}$)100 % = (γ /$\bar{}$)100 % = (γ /$\bar{\alpha}$)100.

Table VII Statistical parameters of VCG lead systems net directional errors

Data from	$\overline{xY}$	$\overline{xZ}$	β	$\overline{yX}$	$\overline{yZ}$	β	$\overline{zX}$	$\overline{zY}$	β
McFee Parungao H	−007	−017	1?	001	−001	2	−002	−014	10
Frank, H	−023	021	?7	00?	−.005	7	−008	−006	11
McFee Parungao I	−002	−.035	17	−004	−001	2	−.006	−02"	12
Frank, I	−0?4	017	?0	−003	−014	10	−0?4	−014	22

Lower case indicates e citat on direction upper case ind ates lead orientat on β are n t polar angles in degrees.

Table VIII Inverse solutions to three unit components of single dipoles (results same for least and quadprog algorithms)

Transfer coefficients used		Position 3			Position 5			Position 6		
Inverse solution	*Forward solution*	*X*	*Y*	*Z*	*X*	*Y*	*Z*	*X*	*Y*	*Z*
Homogeneous	Homogeneous	1 00	1 00	1 00	1 00	1 00	1 00	1 0	1.00	1 00
Inhomogeneous	Inhomogeneous	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00
Homogeneous	Inhomogeneous	1 37	1 65	92	1 64	2 50	60	1 45	1 09	1.24
Inhomogeneous	Homogeneous	76	65	1 01	72	37	1 19	68	.84	78

axial The improvement in the UVM model toward equal average sensitivities after intro ducing inhomogeneities appears to be fortuitous but similar in the Frank and axial systems

The standard deviations σ σ σ of the lead sensitivities are also shown in Table V in sensi tivity units and as percentages of the means $\bar{X}$ $\bar{Y}$ and $\bar{Z}$ These indicate reasonably small varia tions from point to point in the heart in the homogeneous case for the x and y directions with larger changes in z The large σ in the McFee system reflects primarily the large error in a single heart location very close to the body surface (Pos 14) and correspondingly, very close to one electrode of the triangular array on the anterior chest wall The standard deviations with the exception of the Frank z lead increase roughly by a factor somewhat greater than two when inhomogeneities are introduced The large scatter in Frank z components was relatively

Table IX Inverse solutions to six unit components of two dipoles (results same for 'least' and 'quadprog' algorithms)

Transfer coefficients used		*Positions 3 and 5*					
Inverse solution	*Forward solution*	X_3	Y_3	Z_3	X_5	Y	Z_5
Homogeneous	Homogeneous	1 00	1 00	1 00	1.00	1 00	1 00
Inhomogeneous	Inhomogeneous	1 00	1 00	1 00	1 00	1 00	1 00
Homogeneous	Inhomogeneous	1 02	2 00	1 51	1 84	1 62	55
Inhomogeneous	Homogeneous	96	46	62	54	.55	1 21
		Positions 3 and 6					
		X	Y_3	Z_3	X	Y	Z
Homogeneous	Homogeneous	1 00	1 00	1 00	1 00	1 00	1 00
Inhomogeneous	Inhomogeneous	1 00	1 00	1 00	1 00	1 00	1 00
Homogeneous	Inhomogeneous	2 02	1 15	1 53	71	1 61	1 01
Inhomogeneous	Homogeneous	49	1 3[illegible]	62	82	19	1 08
		Positions 5 and 6					
		X_5	Y	Z_5	X_6	Y	Z
Homogeneous	Homogeneous	1 00	1 00	1 00	1 00	1 00	1 00
Inhomogeneous	Inhomogeneous	1 00	1 00	1 00	1 00	1 00	1 00
Homogeneous	Inhomogeneous	2 41	1 93	87	78	1 17	1 52
Inhomogeneous	Homogeneous	18	54	94	1 04	95	65

Table X Inverse solutions to nine unit components of three dipoles ('least' algorithm)

Transfer coefficients used		*Positions 3 5 and 6*								
Inverse solution	*Forward solution*	X	Y	Z	X	Y	Z	X	Y	Z
Homogeneous	Homogeneous	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00
Inhomogeneous	*Inhomogeneous*	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00
Homogeneous	Inhomogeneous	2 96	68	80	1 33	1 68	2 10	−06	2 46	74
Inhomogeneous	Homogeneous	−98	3 23	1 36	1 34	27	−20	1 32	−73	1 60

unchanged by the inhomogeneities but the sensitivity at the unusual point in the McFee system being in a region of the heart unshielded by lung rose from a factor of almost 2 greater than the mean x sensitivity in the homogeneous case to almost 8 in the inhomogeneous case point 14, Tables I and III In general, the change of variability in lead sensitivity from the homogeneous to the inhomogeneous configuration roughly corresponds to the quantitative theoretical estimate of McFee and Rush,[20] who predicted a maximum difference in sensitivity with location that would vary over a range of 2 5 to 1 The exact comparison between theory and experiment is difficult because of the variations in sensitivity which exist even in the homogeneous torso An indication of the comparison can however, be obtained from the *y* lead This is the closest to ideal in the homogeneous case in the McFee Parungao system and has a standard deviation only 8 per cent of the mean The range in *y* transfer coefficient values is almost 2 to 1 in the inhomogeneous case as compared to the 2 5 to 1 predicted theoretically Moreover the positions where the extremes are found in the inhomogeneous case have equal sensitivity in the homogeneous torso indicating that the 2 to 1 range is due entirely to the inhomogeneities Considering that only 13 positions in the ventricles of the heart have been considered (so that the worst possible

Table XI Inverse solutions to nine unit components of three dipoles (quadprog algorithm)

Transfer coefficients used		*Positions 3 5 and 6*								
Inverse solution	*Forward solution*	X	Y	Z	X	Y	Z	X	Y	Z
Homogeneous	Homogeneous	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Inhomogeneous	Inhomogeneous	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Homogeneous	Inhomogeneous	[illegible].85	.73	.81	1.41	1.[illegible]0	2.02	.00	2.33	.79
Inhomogeneous	Homogeneous	.00	2.[illegible]0	1.14	.68	.28	.54	1.14	.00	1.10

Table XII Inverse solutions to the magnitudes of dipoles with fixed orientation (unit strength components) (Results same for least and quadprog algorithms)

Transfer coefficients used		*Pos 3*	*Pos 5*	*Pos 6*	*Pos 3 and 5*		*Pos 3 5 and 6*		
Inverse solution	*Forward solution*	*D*	*D*	*D*	*D*	*D*	*D*	*D*	*D*
Homogeneous	Homogeneous	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Inhomogeneous	Inhomogeneous	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Homogeneous	Inhomogeneous	1.27	1.54	1.27	1.1[illegible]	1.67	1.[illegible]2	1.61	.93
Inhomogeneous	Homogeneous	.76	.62	.7	.9[illegible]	.50	.44	.62	1.0[illegible]

Ds are dipole strengths

case may not have been seen) the correspondence between the measured 2.1 and the theoretical 2.5:1 seems remarkably close. It is not suggested that current flow in the torso corresponds accurately to that in the ideal theoretical model but that the theory predicts fairly well the range of current density magnitudes likely to be caused by the inhomogeneities.

The analysis of angle errors is complicated by the fact that the only convenient measure is a polar angle which is a form of magnitude (i.e. polar angles are ambiguous with respect to meridian lines); complete angle information in the form of cartesian vector components is found in Tables I through IV. A review of the mean angular errors as displayed in Table VI $\bar{\alpha}$, $\bar{\alpha}_y$ and $\bar{\alpha}$ shows the McFee system somewhat superior to the Frank system. Both systems tend to deteriorate in the inhomogeneous case with the mean angular errors approximately doubling. The standard deviations γ, γ_y and γ in the polar angles also show significant increases in the inhomogeneous case compared to the homogeneous.

Table VII shows that the angular errors displayed in Table VI tend to be systematic in the x leads and only slightly less so in the z leads. The systematic errors in the y leads are negligibly small in the axial system and relatively small also in the Frank system. This can be determined by comparing the $\bar{\alpha}$s in Table VI which are roughly equivalent to the average of the polar angle magnitudes with the βs of Table VII which are *polar angles formed from the resultants of the off diagonal components*.

The inverse multiple dipole solutions from the least mean square and quadprog programs are revealing in that they indicate a very strong influence of the inhomogeneities on the inverse solution. One viewpoint about this suggests that the difference between the homogeneous and inhomogeneous coefficients is a form of noise which corrupts the quality of the inverse solution in the clinical situation. The use of correct or more nearly correct transfer coefficients would correspond to a reduction in that noise and an increase in the accuracy of the inverse solution.

In the progression from Tables VIII to IX to X the number of components determined in each inverse solution increases from 3 to 6 to 9 while the number of sample points on the surface remains constant at 20. As would be anticipated the deviation of the inverse values from the constant unit dipoles used in the forward solution increases with the increase in components being calculated. The gross errors however in the inverse solution that appear in the third and fourth rows of all these tables result from the effects of inhomogeneities and are common to all

cases studied In Table VIII, for example the inverse solution ranges from 6 to 2 5 in the third row and from 37 to 1 19 in the fourth, even though these *inversions involve only three dipoles* (or three components of one dipole) in each case In Table IX where the inversions are to six dipole components (dipoles at two locations, each with three components), the range is from 55 to 2 4 in the third row and from 19 to 1 35 in the fourth In Table X, the errors are so large in rows 3 and 4 that one third of the terms of row 4 which are positive when producing the forward solution *become negative in the inverse* In Table XI, which employs non negativity constraints most negative terms are set to zero but there is also a small but clearly discernible over all improvement of the other values in the sense that the range of inverse values is reduced toward the common dipole strength used in the forward solution

Table XII displays the results of using dipoles *oriented so as to make equal angles with the* cartesian coordinate axes The first three columns show inverse solutions when one dipole is used in each forward and inverse calculation The fourth and fifth columns show results using a pair of dipoles while the sixth column shows the results for three dipoles simultaneously The results are *similar to the previous cases particularly to* Tables VIII and IX since no negative values appear in the least mean square solution Many additional calculations similar to those reported above have been made the over all picture of the results however is much the same as that shown by the tables presented

Judging from the tabulated results it would seem impossible to suppose that a clinical inverse *solution using homogeneous coefficients could be* useful Indeed that was conceded to be the case by most workers in the field until the quadratic scheme, with its additional polarity constraints was introduced Even with such constraints the data shown here are not of a sort to inspire confidence in the ultimate success of an inverse solution using homogeneous case transfer coefficients

Before drawing any final conclusions however several additional factors must be considered In the first place the simulations of heart activation used here consist of only a *few dipoles with* arbitrary locations, strengths and orientations These represent only a fraction of all the actual possibilities, in particular, more realistic source arrangements might yield more accurate results Second, the basic transfer coefficient data used are not completely noise free, although great pains have been taken to make them as accurate *as possible This noise has no effect on the first* two rows of the tables where errors of the forward solution are cancelled in the inverse solution The errors do however, affect rows 3 and 4 because there the noise appearing in the transfer coefficients affects the forward and inverse solutions independently Moreover, there is no specific way *to determine the extent of the noise contribution* to the inverse solution Finally the errors large *as they are may still permit an inverse solution* more informative in some respects than the conventional 12 lead ECG The claims of the Alabama group, which has applied the quadratic programming technique to the inverse solution clinically are rather modest They found that the dipoles representing the various heart regions *were turned on only once during the heart cycle* and furthermore that the areas under the dipole strength versus time curves were proportional to the volume of the heart muscle represented [1] It is this latter feature, apparently that makes their inverse solutions useful for the diagnosis of ventricular hypertrophy

In summary this paper contributes to the understanding of the influence of inhomogeneities on the ECG by analyzing data obtained from a torso model which can be used with and without inhomogeneities As with all such studies the extent of inhomogeneity influence must be considered with respect to specific objectives So *far as VCG leads are concerned the data shows* that inhomogeneities roughly double the already significant imperfections of the Frank and McFee leads that the z lead is potentially the most troublesome and that the order of magnitude of the variations corresponds roughly to that predicted theoretically These *imperfections ap pear to be of sufficient gravity to explain* the failure of resolver schemes to normalize heart data with respect to rotation [1] With regard to inverse solutions it has been found true here as elsewhere that inversions to complex generators are possible *with noise free data* With inhomogeneity noise very large errors are introduced *into the inverse solution* Since inverse solutions under these conditions have been found useful nevertheless the prospect of improvement if lead

transfer coefficients could be tailored to individuals while taking body inhomogeneity and anisotropy into account seems favorable

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Mechanism of hypotensive effect during beta-adrenergic blockade in hypertensive patients

HEMODYNAMIC AND RENIN RESPONSE TO A NEW CARDIOSELECTIVE AGENT, TENORMIN OR ICI 66 082

A Amery, M D
L Billiet M D
A Boel, M Sc
R Fagard, M D
T Reybrouck, M S
J Willems M D
Leuven Belgium

Beta adrenergic blocking drugs are used in the treatment of hypertension (for references, see Conway[1]) but their mode of action is not understood It has been suggested that it may be related to the decrease in cardiac output to changes in total peripheral resistance,[2] or to the fall in plasma renin activity[3]

The action of a beta blocker is complex Not only may there be differences in selectivity for individual tissues but there are actions other than beta blockade such as intrinsic sympathomimetic activity and quinidine like or membrane stabilizing effects Therefore, for this study we chose the new beta blocker 4 (2 hydroxy 3 isopropylaminopropoxy)phenyl acetamide or Tenormin * because in animal experiments it has been shown to be devoid of sympathomimetic and quinidine like activities Furthermore its beta blocking action is cardioselective with little effect on bronchi and blood vessels,[4] and it would also be likely, according to the theory of Assaykeen,[5] to have little effect on renin release

Methods

The study was carried out in two phases the major part taking place in hospital with a follow up in some patients on an outpatient basis

From the Department of Medicine University of Leuven Belgium

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Reprint requests A Amery M D Professor in Medicine University Hospital St Raphaël II 3000 Leuven Belgium

*The trade name of this agent is used throughout this study because a chemical name has not yet been accepted

Selection of patients Thirty eight patients in an age range between 20 and 65 years, with renal or essential hypertension were recruited for this study, their consent having been obtained after the nature of the test and the procedures to be used had been explained to them The study complied with the code of ethics of W H O for human experimentation (Declaration of Helsinki) All antihypertensive treatment was stopped for at least 3 weeks The patients were thereafter hospitalized for about 5 weeks No patient was on rauwolfia derivatives just prior to this study During an initial run in period on placebo the patients had laboratory studies including hemogram urinanalysis, fasting blood sugar serum creatinine electrolytes bilirubin plasma renin urinary catecholamines, electrocardiogram pulmonary function tests chest x ray and hemodynamic investigations All patients previously had an intravenous pyelogram and some a renal arteriogram if indicated Patients with any of the following were excluded signs of heart failure, history or signs of bronchospasm, hematological, hepatic or nonhypertensive cardiac disease, possibility of pregnancy by history a recent cerebrovascular accident a creatinine clearance below 30 ml per minute or insulin requiring diabetes mellitus Only patients with a diastolic blood pressure between 90 and 139 mm Hg at the end of the run in period in hospital were admitted into the study

The hospital phase This part of the study was divided into five periods 0 to 4 , each of 1 week s

duration Throughout the study patients received six tablets (two tablets three times a day) each day These were identical in taste shape, and color During the first period 0 they received placebo tablets during period 1 75 mg per day of Tenormin in period 2 150 mg per day in period 3 300 mg per day finally in period 4 600 mg per day Although this was the general plan of the study variation was allowed in exceptional circumstances In some patients the placebo period was extended to 2 weeks if a steady blood pressure level had not been achieved earlier In five patients whose blood pressure was very high on placebo treatment was started immediately with 150 mg of Tenormin In 11 patients the final daily dose of 600 mg was not achieved either because the diastolic blood pressure fell below 85 mm Hg (seven patients) or the recumbent heart rate fell below 45 beats per minute (two patients) or clinical signs of fluid retention emerged (three patients) All patients were placed on a constant sodium diet resulting in an average urinary sodium excretion of 123 4 ± 51 4 mEq per day during the placebo period and 137 6 ± 37 7 mEq per day during the final hospitalization period They were up and about throughout the day and physically active while they were in hospital and they were allowed to go home for about 30 hours each weekend

Methods of measurement

1 **Blood pressure** Blood pressure was recorded four times daily in the morning recumbent before rising and then in the standing position after lunch and supper first standing and then after 5 minutes bed rest and just before going to bed again standing and recumbent The patients measured their own blood pressure with the Autosphig the reliability of these measurements was checked daily during the first week and thereafter at weekly intervals by a physician In a few patients whose measurements were not accurate the readings were taken by a nurse Both the nurse and the patients were unaware of the exact nature of the treatment The mean of these eight daily determinations was averaged for the final 3 days of each period

2 **Degree of cardiac blockade** Beta blockade was assessed by measuring the pulse rate in the recumbent position in the morning before rising and before the morning dose of the drug The maximum heart rate was also determined on the bicycle ergometer with a multistage uninterrupted exercise test up to the point of voluntary maximal exercise capacity as has been described previously[4] During the first phase this test was performed at weekly intervals on one of the final 2 days of each treatment period

3 **Hemodynamic measurements** Hemodynamic measurements were carried out in 28 of the subjects near the end of the placebo period and during the final hospitalization period on the drug A venous catheter (Swan Ganz 93 110 5F) was introduced percutaneously through an intramedicut Argyle catheter in the anticubital vein and floated up to the pulmonary artery Pulmonary wedge pressures were obtained by floating the catheter into a small artery and inflating the balloon The brachial artery was punctured with a Teflon needle (Dameco model 110 by 82 mm) to measure the intra arterial

Table I Some characteristics of the patients at entry (during placebo period)

Total number	38
Sex	
Male	17
Female	21
Age (mean and S D) (yr)	43.9 ± 12.5
ECG	
Normal	20
Possible left ventricle hypertrophy	10
Left ventricle hypertrophy	8
Eye fundus grade according to Keith Wagener	
0	3
1	21
2	12
3	1
4	1
Blood pressure measured by the physician on admission to the hospital	
Systolic	202.1 ± 23.4
Diastolic	125.8 ± 12.7
Creatinine clearance (mL/min)	70.3 ± 19.5
Etiology of hypertension	
Essential	25
Nephritis	8
Renovascular	5
WHO classification of hypertension	
Stage I	17
Stage II	15
Stage III	5
Malignant hypertension	1
Renin subgroups	
High	8
Normal	21
Low	8
Results not available in placebo period	1

Table II Blood pressure and heart rate during the different hospitalization periods

	Period 0	Period 1	Period 2	Period 3	Period 4
	Daily dose of Tenormin (mg)				
	0	75	150	300	600
Systolic blood pressure throughout the day (mm Hg)					
$\bar{x}$	180.3	157.3	153.8	152.1	151.9
S D	26.2	23.6	25.7	30.0	25.5
N*	38	33	37	37	27
p† compared to period 0	–	< 0.001	< 0.001	< 0.001	< 0.001
p compared to period 3	< 0.001	< 0.001	< 0.001	–	> 0.1
Diastolic blood pressure throughout the day (mm Hg)					
$\bar{x}$	118.0	102.0	97.4	94.6	96.3
S D	13.6	11.4	11.5	12.7	13.8
N	38	33	37	37	27
p compared to period 0	–	< 0.001	< 0.001	< 0.001	< 0.001
p compared to period 3	< 0.001	< 0.001	< 0.001	–	> 0.1
Pulse rate recumbent in the morning (beats/min)					
$\bar{x}$	80.3	67.5	63.1	59.8	60.2
S D	9.8	8.5	6.4	6.6	6.5
N	38	32	36	36	27
p compared to period 0	–	< 0.001	< 0.001	< 0.001	< 0.001
p compared to period 3	< 0.001	< 0.001	< 0.001	–	> 0.1
Maximum exercise heart rate (beats/min)					
$\bar{x}$	170.2	134.1	125.9	116.5	112.7
S D	20.7	18.0	20.6	20.3	16.7
N	35	30	34	34	27
p compared to period 0	–	< 0.001	< 0.001	< 0.001	< 0.001
p compared to period 3	< 0.001	< 0.001	< 0.001	–	0.01 0.002

*N represents the number of patients in whom this result is available

†p was calculated with the t test for paired observations in those patients where results were available for both periods to be compared

blood pressure, and for blood sampling After introduction of the catheter the heart rate, O_2 consumption and CO_2 production were measured continuously with a Siregnost (Siemens Germany) The pulmonary and brachial artery pressures were registered on a recorder (Mingograph 81), using the Elema Schonander pressure transducer with 5 cm below sternal edge as zero level The cardiac output was measured by the direct Fick method after 30 minutes rest in lying position

4 Plasma renin level The renin concentration in plasma was determined on defrozen plasma using the method described by Skinner[7] (normal range in our laboratory, 8 to 25 Skinner *U per milliliter*) Blood for determination of plasma renin was withdrawn in the morning before the patient arose from bed at the end of each of the five periods during stay in hospital A 10 ml quantity of venous blood was taken into an ice cooled tube containing 0.2 ml of EDTA (60 mg per milliliter), centrifuged in the cold and the plasma frozen to –20° C The values for the renin determinations of the patients studied here did not fall into a normal Gaussian distribution The results are therefore expressed in log of Skinner U per milliliter (log Skinner U) since a normal distribution was then obtained The high and low renin subgroups represented the upper and lower 22 per cent of this distribution

Outpatient phase Fifteen patients were able to attend the outpatient clinic regularly and were followed for 12 weeks The patients measured their blood pressure twice daily at home, and the averages of the 5 last days were calculated at each outpatient visit They were seen at 3 weekly intervals in the outpatient clinic and some performed a multistage exercise test at the sixth ninth, and twelfth week of the outpatient follow up in order to test the degree of beta blockade During the first 6 weeks they continued to take

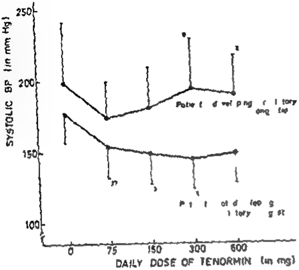

Fig 1 Systolic blood pressure during treatment with Tenormin

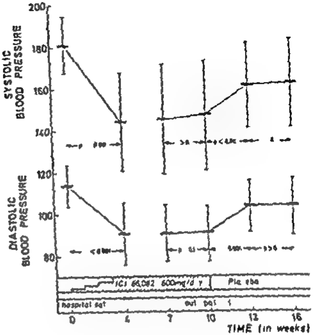

Fig 2 Blood pressure changes during treatment of hypertensive patients with ICI 66 082 (n = 15)

their individual full dose of the drug and during the second 6 weeks they received a placebo

Results

A Characteristics of the patients Of the 38 patients who entered the study 25 were thought to have essential hypertension (Table I) The severity would be classified as moderate to severe and the mean creatinine clearance of 70 ml per minute reflected this Eight patients were classified as having a high renin and another eight had an unusually low plasma renin concentration

B Effect on blood pressure The average blood pressures measured throughout the day during the last 3 days of each hospitalization period are shown in Table II Blood pressure decreased significantly on treatment with 75 mg daily and it fell progressively with increasing doses up to 300 mg per day (Fig 1) The average fall in pressure was 28 4/21 8 mm Hg No signs or symptoms of orthostatic hypotension were observed

During the course of this study six patients developed signs of fluid retention with an increase in the jugular venous pressure liver enlargement, and ankle edema pulmonary rales were not detected The systolic blood pressure response of these patients compared to the remainder is illustrated in Fig 1 This shows that the blood pressure fell during the first period but rose again as fluid retention occurred In these patients a low sodium diet and 50 mg per day of chlorthalidone given with the same dose of the beta blocker caused the blood pressure to decrease again The data on combined therapy have not been used in computing the results of therapy

The blood pressure in the 15 patients who were continued on treatment in the outpatient phase remained under control for the 6 weeks (Fig 2) As they reverted to placebo the blood pressure significantly increased from 147 3 ± 26 1/91.5 ± 13 2 mm Hg to 160 8 ± 20 3/103 1 ± 12 5 mm Hg after 3 weeks on placebo and finally to 161 5 ± 20 9/103 7 ± 12 8 mm Hg after 6 weeks on placebo

C Degree of cardiac beta blockade As can be seen from Table II the pulse rate was significantly decreased during the treatment with 75 mg daily Since this rate was determined before the morning dose of drug some degree of beta blockade had evidently been achieved over night

Maximum exercise heart rate was significantly decreased on a daily dose of 75 mg but a small but significant additional decrease in maximum exercise heart rate was observed on increasing the daily dose from 300 to 600 mg

As noted earlier blood pressure fell with increasing doses of Tenormin and over all there was a significant correlation between the degree of beta blockade and the change in diastolic blood pressure (Fig 3)

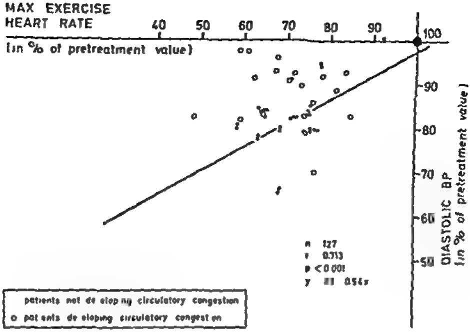

Fig 3 Correlation between maximum exercise heart rate and diastolic blood pressure during beta blockade with Tenormin

D Influence of Tenormin on hemodynamic measurements at rest Highly significant decreases in mean heart rate mean cardiac output and mean brachial artery pressure were observed in the patients (n = 28) who were subjected to cardiac catheterization No significant change was found in mean total peripheral resistance The pressures in right atrium right ventricle pulmonary artery and pulmonary wedge did not change significantly

Four of the six patients who developed clinical signs of fluid retention were catheterized before and during therapy The changes between the placebo and final inpatient period in mean brachial artery pressure (from 144 5 ± 13 9 to 148 0 ± 28 2 mm Hg) were not significant The mean cardiac output decreased from 4 9 ± 1 1 to 4 4 ± 1 1 L per minute the mean total peripheral resistance rose from 30 3 ± 8 1 to 36 1 ± 14 7 U the mean stroke volume increased from 65 7 ± 20 6 to 75 2 ± 23 7 ml (0 1 > p > 0 05) the mean right atrial pressure increased from 3 3 ± 0 6 to 7 0 ± 2 0 mm Hg, and the end diastolic right ventricular pressure increased from 4 3 ± 1 6 to 7 6 ± 4 2 mm Hg the differences in all measurements were statistically not significant (p > 0 01) The mean pulmonary artery pressure rose significantly however from 14 6 ± 4 7 to 24 0 ± 3 9 mm Hg (p < 0 01)

Inspection of individual data in the patients who did not develop signs of fluid retention showed that no significant correlation was found between the decrease in cardiac output during the drug treatment and the fall in mean brachial artery pressure On the other hand, a significant correlation was found between the percentage decrease in mean brachial artery pressure and the change in calculated total peripheral resistance (Fig 4)

E Influence on plasma renin concentrations The plasma renin concentration determined on blood drawn from 33 patients recumbent in the morning before rising decreased from 1 180 ± 0 302 to 1 061 ± 0 277 log Skinner U per milliliter in the final hospitalization period (p < 0 02) this corresponds to a decrease from 15 1 Skinner U per milliliter during the placebo period to 11 5 Skinner U per milliliter during the final hospitalization period

No significant correlation was found between the hypotensive effect and the changes in these plasma renin levels

Discussion

Before analyzing the relative role of beta blockade hemodynamic factors and the renin angiotensin system in producing the hypotensive effect some general remarks concerning the outline of the present study should be made

A General remarks concerning the inpatient study Several constraints were accepted to allow this study to be undertaken and it is appreciated that these may have had some influence on the results

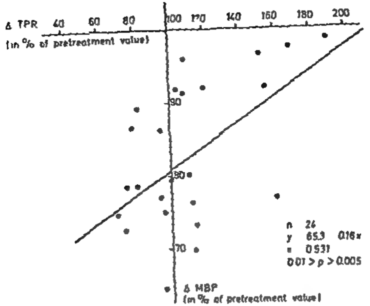

Fig 4 Changes in total peripheral resistance (TPR) and mean blood pressure (MBP) during treatment with Tenormin

1 The investigation was not planned as a double blind study since its main purpose was the study of the mechanism of the hypotensive effect of beta adrenergic blockade The physicians on the wards were aware of the nature of the treatment but all tablets were identical in taste shape and color and the persons who measured the blood pressure and the pulse rate were unaware of the precise nature of the tablets the patient was taking or the dose Thus these measurements at least were made under blind conditions

2 The periods of treatment of the study were always in the same chronological order with increasing dose of drug and they were short Consequently the full effect of each dose may not have been achieved and the drug requirement may have been overestimated

3 The hemodynamic measurements and renin estimations were made while the patients were in hospital and it is possible that rest in hospital produced a progressive influence particularly on blood pressure A placebo period however preceded active treatment and in any case where the blood pressure was still decreasing on the fifth day of the placebo period it was extended until a constant baseline was reached Thus there was no change in blood pressure level in the 2 days prior to treatment with active drug.

The patients were given a preliminary run with the exercise and pulmonary investigations the day before the measurements were made but it is possible that as the study proceeded they became less anxious and that this could have contributed in part to the decrease of heart rate oxygen consumption and perhaps other parameters which occurred on treatment with Tenormin

4 Since the patients performed exhausting exercise tests at weekly intervals an element of training may have influenced certain parameters

5 It should also be realized that the number of patients studied is small and that patients with hypertension of differing severity and etiology were included.

Although the quantitative importance of these constraints upon the results cannot be assessed the outpatient phase made it possible to evaluate effects on the heart rate and blood pressure under more natural conditions

B Hypotensive effect during beta blocking with Tenormin The beta blocker studied here--Tenormin--has a clear hypotensive effect The blood pressure decreased over all during the hospitalization periods by an average of 28/22 mm Hg and if the patients who developed fluid retention were excluded the decrease in blood pressure was 34/26 mm Hg This is similar to the blood pressure decrease of 29/17 mm Hg observed by Hansson and associates who treated 20 patients with 100 to 200 mg per day of the same drug.

The demonstration that blood pressure rose

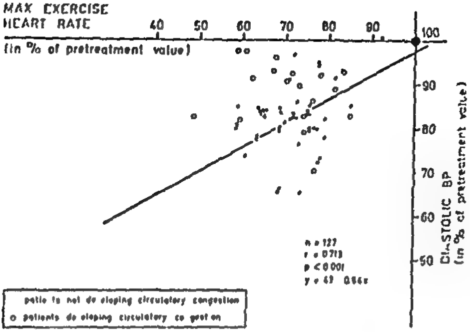

Fig 3 Correlation between maximum exercise heart rate and diastolic blood pressure during beta blockade with Tenormin

D Influence of Tenormin on hemodynamic measurements at rest Highly significant decreases in mean heart rate, mean cardiac output and mean brachial artery pressure were observed in the patients (n = 28) who were subjected to cardiac catheterization. No significant change was found in mean total peripheral resistance. The pressures in right atrium, right ventricle, pulmonary artery, and pulmonary wedge did not change significantly.

Four of the six patients who developed clinical signs of fluid retention were catheterized before and during therapy. The changes between the placebo and final inpatient period in mean brachial artery pressure (from 141.5 ± 13.9 to 148.0 ± 28.2 mm Hg) were not significant. The mean cardiac output decreased from 4.9 ± 1.1 to 4.4 ± 1.1 l per minute, the mean total peripheral resistance rose from 30.3 ± 8.1 to 36.1 ± 11.7 U, the mean stroke volume increased from 65.7 ± 20.6 to 75.2 ± 21.7 ml (0.1 > p > 0.05), the mean right atrial pressure increased from 3.3 ± 0.6 to 7.0 ± 2.0 mm Hg, and the end diastolic right ventricular pressure increased from 4.4 ± 1.6 to 7.6 ± 4.2 mm Hg, the differences in all measurements were statistically not significant (p > 0.01). The mean pulmonary artery pressure rose significantly, however, from 11.8 ± 1.7 to 21.0 ± 3.9 mm Hg (p < 0.01).

Inspection of individual data in the patients who did not develop signs of fluid retention showed that no significant correlation was found between the decrease in cardiac output during the drug treatment and the fall in mean brachial artery pressure. On the other hand, a significant correlation was found between the percentage decrease in mean brachial artery pressure and the change in calculated total peripheral resistance (Fig 4).

E Influence on plasma renin concentrations The plasma renin concentration, determined on blood drawn from 13 patients recumbent in the morning before rising, decreased from 1.180 ± 0.302 to 1.061 ± 0.277 log Skinner U per milliliter in the final hospitalization period (p < 0.02); this corresponds to a decrease from 15.1 Skinner U per milliliter during the placebo period to 11.5 Skinner U per milliliter during the final hospitalization period.

No significant correlation was found between the hypotensive effect and the changes in these plasma renin levels.

Discussion

Before analyzing the relative role of beta blockade, hemodynamic factors, and the renin angiotensin system in producing the hypotensive effect, some general remarks concerning the outline of the present study should be made.

A General remarks concerning the inpatient study Several constraints were accepted to allow this study to be undertaken and it is appreciated that these may have had some influence on the results.

patients treated with propranolol which was not reported by Tarazi and Dustan our data indicate that blockade of the tachycardia produced by maximal exercise was nearly complete It is also possible that hypertensive patients show a greater variability in their response to blocking agents than is presently appreciated It should also be remembered that the number of patients studied here and in other studies is limited and that the hypertension was of different degrees of severity and etiology

Looking at individual results the decrease in the mean brachial artery pressure was not related to the decrease in resting cardiac output but was related to the changes in the total peripheral resistance (Fig 4) This may indicate that the reaction of the peripheral vessels rather than the cardiac output will determine whether the drug will provoke a major decrease of the blood pressure Franciosa and associates also felt that their data did not support the view that reduced cardiac output is the important factor in reducing blood pressure on treatment with timolol Tarazi and Dustan using propranolol came to the same conclusions

Taking their results and our own it appears that the administration of beta blocking agents usually produces a fall in cardiac output and that the patients in whom the drug causes a large fall in blood pressure do not show a large increase in peripheral resistance The mechanism responsible for the changes in resistance are unknown

In interpreting these results one should realize that the peripheral resistance was not measured directly but calculated as a function of flow and pressure Since a direct measurement of peripheral resistance is not available it is reasonable to accept this calculation as a reflection of the overall changes in the peripheral vasculature

E Role of the plasma renin angiotensin system in producing the hypotensive effect of Tenormin Buhler and associates have shown in 47 patients with essential or renal hypertension that the hypotensive action of propranolol closely correlated with the degree of suppression of plasma renin This work was confirmed by this group in 73 patients with essential hypertension[3] and Castenfors and associates also reported a significant correlation between the change in systolic blood pressure and the plasma renin activity in 17 patients on diuretic therapy who were treated with alprenolol

Using the beta blocker Tenormin we found only a small decrease (26 per cent) in the plasma renin concentration whereas Buhler and associates[3] using propranolol found a 62 per cent decrease in plasma renin activity This difference could result from several factors Tenormin is cardioselective and thus may have had a limited ability to suppress renin Johns and Singer[20] studied the comparative effectiveness of propranolol and Tenormin in inhibiting the renin release from the kidney resulting from renal nerve stimulation in the cat and found Tenormin about five times less effective than propranolol

There were of course methodological differences between our study and those of others Specifically we measured plasma renin concentration as opposed to "activity" and we were interested in the renin level in the unstimulated state at rest While our results cannot therefore be compared with those of Buhler and associates they do show that a beta blocking drug can lower blood pressure with only a small effect on plasma renin concentration Furthermore the hypotensive effect was not related to changes in plasma renin concentration This area clearly requires further investigation

F Fluid retention during treatment with beta blockers During the treatment of the 38 patients with Tenormin six developed increased jugular venous pressure a positive hepatojugular reflux liver enlargement and even ankle edema pulmonary rales were not noted Compared with the other 32 patients these six patients had somewhat higher blood pressure during the run in period The systemic blood pressure (Fig 1) decreased during the first week and increased again as the signs of circulatory congestion developed The same loss of blood pressure control when fluid retention occurs has been observed by Finnerty with other antihypertensive drugs

The true incidence of fluid retention with Tenormin remains to be established and to be compared with that seen with other beta blockers and with other nondiuretic antihypertensive agents Nevertheless the emergence of six cases with fluid retention was unexpectedly high and it stresses the need to be on one's guard for this in the treatment of hypertension with this type of agent

Summary

The mechanism of the hypotensive effect during beta adrenergic blockade in hypertension was studied in 38 patients with renal or essential

Table III Hemodynamic parameters at rest recumbent

	Run in period	Final inpatient period	Difference between both periods	p between both periods
Heart rate (beats/min)				
x̄	85 8	58 7	−27 4	
S D	12 7	6 5	11 0	
N	28	28	28	< 0 001
Mean brachial artery pressure (mm Hg)				
x̄	139 5	119 7	−19 7	
S D	14 4	22 3	17 5	
N	28	28	28	< 0 001
Cardiac output (L/min)				
x̄	5 5	4 3	− 1 2	
S D	1 7	1 1	1 21	
N	28	29	28	< 0 001
Stroke volume (L/min)				
x̄	65 5	73 4	+ 8 4	
S D	18 1	13 0	10 9	
N	28	28	28	< 0 001
Total peripheral resistance (conventional units)				
x̄	27 7	29 7	+ 2 0	
S D	10 1	11 4	8 9	
N	28	28	28	> 0 1
Mean atrial pressure (mm Hg)				
x̄	3 02	2 99	− 0 21	
S D	2 01	2 57	2 8	
N	23	23	23	> 0 1
End diastolic right ventricular pressure (mm Hg)				
x̄	2 87	2 61	− 0 11	
S D	2 8	3 6	3 6	
N	23	23	23	> 0 1
Mean pulmonary artery pressure (mm Hg)				
x̄	13 0	13 8	+ 0 8	
S D	5 4	7 0	5 7	
N	25	25	25	> 0 1
Wedge pressure (mm Hg)				
x̄	7 46	7 46	0	
S D	4 8	2 8	5 7	
N	12	12	12	> 0 1

again after 3 weeks withdrawal of the drug confirms that the lowering of blood pressure by Tenormin is a genuine effect

C Role of beta blockade in producing the hypotensive effect Several tests have been proposed to measure beta blockade namely exercise tachycardia,[9] heart rate response to isoproterenol [10,11] and tachycardia after trinitrin [12]

1 The resting pulse rate is considered to be a poor parameter for the estimation of the degree of beta blockade in the heart as it is influenced by both vagal and sympathetic tone Nevertheless the progressive decline in resting heart rate with increasing doses was proportionately the same as the decline in exercise tachycardia

2 Although the physiological response to exercise is complex, vagal influence is only slight at higher heart rates [13,14] As can be seen from Table II, an increase of the daily dose from 75 to 150 and to 300 mg produced a significant decrease in the heart rate produced by maximal exercise Increasing the dose to 600 mg did produce a further small but significant reduction in the exercise tachycardia This could indicate that 300 mg per day were not adequate to produce complete beta blockade

As can be seen from Fig 3, a significant correlation was obtained between the blood pressure fall and the degree of beta blockade in the heart This cannot be taken to indicate that the influence of beta blockade on the heart causes the fall in blood pressure but it does indicate that there is a relationship between these effects

D Role of hemodynamic factors in producing the hypotensive effect of Tenormin The pattern of the systemic hemodynamic responses of hypertensive patients to treatment with adrenergic beta blocking agents is not clear Compounds which possess sympathetic stimulating properties in addition to their ability to block betareceptors (such as practolol[15,16] and oxprenolol[17]) appear to have little effect on resting cardiac output yet these drugs have a hypotensive action According to Franciosa and associates[1] during acute or 1 week treatment with another nonselective beta blocking agent—timolol—cardiac output fell and total peripheral resistance increased but after 5 weeks treatment cardiac output had returned to pretreatment values and total peripheral resistance fell slightly Propranolol has been shown to reduce cardiac output and this effect is sustained with continued treatment[4] Peripheral resistance rises initially and then after a period of many months in the patients who show a fall in blood pressure there is a decrease in peripheral resistance

In our study within 1 month of the start of therapy the mean arterial pressure the heart rate and the cardiac output were significantly decreased (see Table III) whereas the calculated total peripheral resistance did not change significantly The reason for these differences from the reported effects with propranolol could be cardioselectivity, or the degree of beta blockade in the

Cannon waves with A-V association

Neil D. Berman, M.D.*
Menashe B. Waxman, M.D.**
Toronto, Ontario, Canada

It is generally accepted that giant A waves, commonly referred to as cannon waves, should be sought in cases of A-V dissociation. Third degree A-V block and some cases of ventricular tachycardia are two classical examples in which these waves may be seen. The proposed mechanism for these waves is a large increase in intra-atrial pressure caused by atrial systole occurring against closed A-V valves. It is less commonly recalled that some A-V associated rhythms may produce cannon waves. We present the following case as an example of sinus rhythm in which markedly prolonged A-V conduction time resulted in atrial systole occurring during ventricular systole of the preceding beat. Thus readily visible and, in fact, palpable cannon waves were produced which would vary in height as A-V conduction varied and would disappear with the development of second degree A-V block.

Case report

A 50-year-old woman was admitted for reassessment of long-standing mitral valve disease. On physical examination she was noted to have cannon waves in the presence of a regular rhythm. There was no evidence of tricuspid valve disease. Furthermore, the cannon waves would at times disappear spontaneously. Fig. 1 shows Lead V. On the left side of the strip the rhythm is regular at a rate of 110 beats per minute and atrial activity is not readily apparent. The QRS complex appears to have an RSR' pattern consistent with right bundle branch block or right ventricular hypertrophy. Clinically, the presence of cannon waves in the jugular venous pulse led us to suspect that there might be atrial activity buried within the QRS complex. The effect of carotid sinus massage is shown. With prolongation of A-V conduction the R' is shown, in fact, to be a P wave with a long PR interval (0.42 second).

Carotid sinus massage further lengthens the PR interval and appears to move the P wave back onto and, in fact, through the preceding QRS (see P wave labeled X, which actually falls before the QRS and fails to conduct). Furthermore, this change could be monitored by observing the venous waves as A-V conduction was altered. Fig. 2 documents these changes. Lead V, the jugular venous pulse, and the brachial arterial pulse were amplified and recorded using Hewlett-Packard contact sensor transducers (Model 21050A) and an Electronics for Medicine DR 12 recorder. Cannon waves are seen with waves 1 through 6. Carotid sinus massage lengthens the P-R interval pushing the P wave into the antecedent QRS complex and increases the height of A wave 6. During A-V block the cannon waves disappear as the atria no longer contract against ventricular systole (waves 7 through 11). With the resumption of A-V conduction small cannon waves reappear (12 and 13).

Cannon waves are then seen (14 through 20) which are of greater amplitude than 1 through 5, because the PR interval of these cycles is still prolonged over the control value.

Conclusions

1. This case illustrates the occurrence of cannon waves with an A-V associated rhythm. Furthermore, this clinical observation and the changes induced by carotid sinus massage effectively corroborated the electrocardiographic interpretation of A-V association with a supraventricular rhythm.

2. The combination of a suitably long PR interval and a rapid heart rate could be expected to produce giant A waves.

3. Ventricular tachycardia or right ventricular pacing with retrograde association could produce identical cannon waves. However, carotid sinus massage, by slowing or blocking retrograde conduction, would alter or eliminate the cannon waves but would not change the ventricular rate. This could therefore distinguish ventricular tachycardia with cannon waves from a supraventricular rhythm with cannon waves.

From the Department of Medicine, University of Toronto, and the Toronto General Hospital, Toronto, Ontario, Canada.

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Reprint requests: Dr. Menashe B. Waxman, Cardiovascular Unit, Toronto General Hospital, 101 College St., Toronto, M5G 1L7, Ontario, Canada.

*Research Fellow, Ontario Heart Foundation.

**Senior Research Fellow, Ontario Heart Foundation.

hypertension using the new cardioselective beta blocker Tenormin

During 5 weeks hospitalization the patients received first a placebo for 5 to 12 days then a 75 mg dose of Tenormin was given daily for 1 week and thereafter the dose was doubled weekly as necessary up to 600 mg daily The blood pressure decreased from 180 ± 26 2/118 ± 13 6 mm Hg on placebo to 151 ± 25 5/96 ± 13 8 mm Hg during the final hospitalization period on Tenormin (600 mg daily) Six patients developed fluid retention and as this occurred blood pressure control was lost

A subsequent follow up on an outpatient basis of 15 of the patients showed that when the active drug was replaced by a placebo blood pressure rose again confirming that the initial fall in blood pressure was a genuine effect

Multistage bicycle ergometer exercise tests were performed at weekly intervals to test the degree of beta blockade and indicated that this was nearly complete when a dose of 600 mg per day was used A significant correlation between the hypotensive effect and the degree of beta blockade assessed by exercise tachycardia was observed

A slight but statistically significant decrease (26 per cent) was observed in the plasma renin concentration measured recumbent in the morning This decrease was however not correlated with the hypotensive effect of the drug

Although the cardiac output decreased significantly (from 5 5 ± 1 7 to 4 3 ± 1 1 L per minute $p < 0.001$) no correlation was found in individual patients between the cardiac output and the blood pressure decrease

On the other hand, for the total group of catheterized patients ($n = 28$) the calculated total peripheral resistance did not change significantly Yet a significant correlation was found between the changes in total resistance and the hypotensive effect This suggests that the reaction of the peripheral vessels rather than the cardiac output decrease determines whether the drug will produce a major decrease of blood pressure in patients with hypertension

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Remission and recovery from chronic, established, complete heart block

David A Rytand M D
Edward Stinson M D
John J Kelly Jr M D
Stanford and San Francisco Calif

Temporary or prolonged return of atrioventric ular (A V) conduction after many years of estab lished complete heart block seems virtually prohibited by the very name of the disorder Such an event does occur however with reports of remission or recovery in five patients with con genital heart block [1] With acquired block pub lished evidence of this phenomenon is much less convincing and concerns only two patients [2, 3]

This is to record observations upon sponta neous recovery in a young man with congenital block and on a brief remission in an elderly one after seven years of acquired established com plete A V block These experiences led us to make inquiries which resulted in documents also to be presented on remissions in three additional elderly patients who had had complete acquired block from four to ten years All observations were made some time ago unfortunately without His bundle recordings

Case reports

Case 1 NA, kindly referred by Ann Purdy M D was born two months prematurely on May 20 1929 When but a few weeks of age he had a heart rate of 5? to 60 and there was a loud apical systolic murmur there was no cyanosis Occa sional brief episodes of syncope were reported up to two years of age but were not observed by a physician Three lead electrocardiograms on April 15 1931 and on May 24 Aug 30 and Sept 20 1933 were alike in showing (Fig 1 *A*) what someone then interpreted as 2 1 A V block the short strips available failed to establish or eliminate the possibility of complete A V block with synchronization (R R 1.?0 1 24 1 42 and 1.32 sec P R 0 16 0 20 0.22 and 0.24 sec., respectively) In June 1936 the heart rate was reportedly 80 to 90 per minute during a febrile bout of pneumonia and empyema.

Nine electrocardiograms from Jan. 9 193? to Jan 1? 1949 showed complete A V block the P P intervals were 0 60 to 0.8? sec the R R intervals were 1.20 to 1 ?8 sec and the ventricular complexes were normal and regular but for the presence of the supernormal phase of conduction in records taken after 1936 (Fig 1 *B*) A V synchronization was present at times

Meanwhile chorea in 1941 was followed by a rough diastolic murmur at the apex for about two years. An early systolic apical murmur was constant and at times an early diastolic sound was heard and recorded Growth and development were normal, as were roentgenograms of the chest This patient is Case 2 of another report in which Fig *2B* shows the wide range of P R intervals of complete A V block recorded on Jan 15 1949

At a pre-induction Army examination in Feb 1949 the heart rate allegedly was normal. This was confirmed March 29 1949 when an otherwise unchanged electrocardiogram showed a rate of 90 per minute with sinus rhythm and P R 0 40 sec An electrocardiogram (Fig 1 *C*) on July 1 1949 was virtually identical, with P R 0 40 sec and rate 75 per minute except for failure of conduction in a single cycle On July 22 1949 complete A V block reappeared with occasional conduc tion in a supernormal phase at R P intervals of 0.50 to 0 60 sec (P P 0 54 R R 1 09 sec) after exercise complete A V block persisted (P P 0 46 R R 0 85 sec) Complete A V block with a supernormal phase of conduction was present in an electro cardiogram Dec [illegible] 1950 (P P 0 77 R R 1 43 sec) the ventricular complexes remained normal and unchanged (Fig 1 *D*)

After 14 asymptomatic years he was examined in Nov 1964 by Dr Richard Merchant who recorded an electrocardiogram which showed sinus rhythm with a rate of 7? per minute a P R interval of 0 40 sec and a QRS of 0 09 sec An occasional *P* wave was blocked when its onset occurred within 0 28 sec of the preceding QRS

In Dec 1965 he entered a hospital because of a fractured right hip Again he denied symptoms of cardiac disease His heart rate was 80 per minute arterial pressure 115/75 The cardiac examination was said to be normal, but no electrocar diogram was recorded.

In Aug 1967 he was examined by one of us. The patient

From the Departments of Medicine (Cardiology Division) and Surgery (Cardiovascular Division) Stanford University School of Medicine Stanford, Calif and the Department of Medicine Presbyterian Hospital, Pacific Medical Center San Francisco Calif

Received for publication Feb 14 1974

Reprint requests Dr David A. Rytand, Department of Medicine Stanford University Medical Center Stanford Calif 94305

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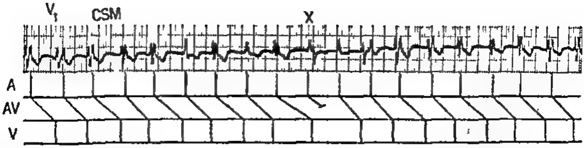

Fig 1 Recording of Lead V and a ladder diagram Carotid sinus massage lengthens the PR interval and moves the P wave onto the preceding QRS (beats 6 and 8) and eventually ahead of the QRS (beat X) At this point second degree A V block develops

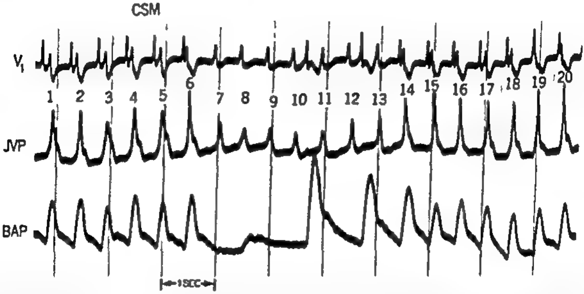

Fig 2 Simultaneous recording of Lead V jugular venous pulse (JVP) and brachial arterial pulse (BAP) Cannon waves are seen during 1 1 A V conduction (waves 1 through 6 and 14 through 20) and disappear during second degree A V block induced by carotid sinus massage (waves 7 through 11) Intermediate cannon waves are seen (waves 12 and 13) as A V conduction resumes

4 In cases of cannon waves due to long PR intervals, further prolongation in PR interval may transiently increase the amplitude of the cannon waves and, as second degree A V block develops, the giant A waves subside Recognition of this provides a simple means of identifying some cases of first and second degree A V block at the bedside

Summary

Under appropriate circumstances cannon waves can occur in the presence of A V associated rhythms Presented here is a case of first degree A V block with cannon waves Recognition of these waves and their behavior aided in diagnosing the patient s rhythm The cannon waves were documented by jugular venous pulse recordings

The authors wish to thank Dr Harold E Aldridge for referring the patient to them and Miss Jacqueline J Smith for her secretarial assistance

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variety (without changes in Leads V through V) and premature beats were rare

The serum potassium was 5 0 mEq per liter before and 4 6 mEq per liter during a trial of chlorothiazide up to 1.5 Gm per day the trial was stopped because of nausea another episode of giddiness, and no improvement in A V block Isuprel, 15 mg in repeated daily doses made him feel jittery caused no improvement and was discontinued Erythrityl tetranitrate produced a sensation of tongue burning and also was stopped No furth r cardiovascular therapy was offered subsequent to Oct 196? when he was hospitalized for gastric retention with an exacerbation of peptic ulcer antacids were used freely

He was examined twice in 1963 four times each in 1964 and 1965 and five times in 1966 Syncope and related symptoms were denied at each visit and on every occasion the ventricular rhythm was regular at rates of 3? to 40 An electrocardiogram of Feb 15 1965 closely resembled that of Sept 28 1960 (there had been inconstant inversion of T waves in Leads V through V) with P P 0 86 sec and R R 2 06 sec and complete A V block A rhythm strip on June 15 19?5 was similar The supernormal phase of conduction was never present X rays of the chest failed to reveal intracardiac calcification

In Dec 1966 he had coryza followed by herpes labialis and on Feb 3 1967 he was given propoxyphene hydrochloride because of low back ache There was no other change in therapy or in his status On Feb 18 1967 however he noticed that his heart rate was an unaccustomed 60 per minute counting it because of the nocturnal sensation of pounding This rate reportedly persisted and two days later he began to have Stokes-Adams attacks for the first time since 196? At examination on Feb 20 1967 the heart indeed was regular at 60 per minute and an electrocardiogram (Fig 2 C) confirmed the presence of 1 1 A V conduction (R R 1 0 sec P R 0 32 sec QRS was unchanged since Feb 15 1965 in showing a *right bundle branch block* pattern and left axis deviation but the unstable T waves in Leads V through V were not so deeply inverted) With sustained deep inspiration 2 1 A V block (Fig 2 *D*) appeared repeatedly (P P 0 84 sec P R 0 ?8 sec) An electrocardiogram Feb 21 1967 was identical to that of the preceding day in all respects including the clear addition of a notch in the P wave of which there had been some earlier suggestion

On Feb 22 19?7 a transvenous fixed rate *pacemaker was* installed On subsequent examination it was functioning perfectly at a rate of 72 per minute No further *syncope or* giddiness had occurred up to a visit on *April* 3 19?6 *but* on Aug 31 1967 he reported occasional orthostatic giddiness and had noted that the pulse was sometimes irregular *The latter* was confirmed by an electrocardiogram (*Fig 2 E*) *which* showed competition of natural and artificial pacemakers with incon tant conduction at a P R *of 0 34 sec* This episode cleared rapidly and on Oct 6 1967 the ventricular *rhythm* was regular again and independent of P waves On Dec 15 19?7 he continued well and the *rhythm* was regular Apparently with chest pain he died suddenly on *Jan 11 1968* At autopsy the pacemaker unit was firing regularly at 6? per minute Calcification of the mitral *fibrous* anulus was present coronary ath rosclerosis was only mild and *there* were no gross anatomic reasons for death. Fibrosis of the A V nodal region and the bundle of His but not of the bundle branches was present (Dr Charles P Bieber)

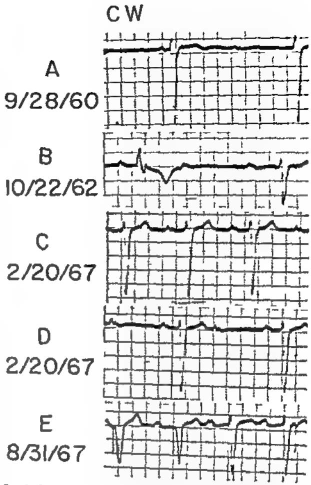

Fig 2 Case 4 CW Lead II throughout The first cycle of *B* is *not premature* A V conduction appears in *C* with 2 1 block in *D*

Case 5 Sk (No 11-62-04) was brought to our attention by Ralph J Spiegl M D who kindly allowed us to summarize his records. He was 63 years of age in 1948 when he *first visited* another physician with a history suggestive of angina pectoris and paroxysmal tachycardia but these never were *present or* prominent subsequently Mild arterial *hypertension* and obesity were the chief findings Nine electrocardiograms from Dec 6 1948 to March 5 1962 were alike *in* showing sinus rhythm rate 50 to 8? P R 0 18 to 0.24 sec *and QRS* 0 08 sec suggestion of P wave notching in Lead 2 prominent Q wave in Leads 3 and aV_F and normal Leads V through V only the last two records showed *prolonged* A V conduction The heart rate was normal in each of a dozen examinations to June 1 196?

Asymptomatic heart block was discovered at another visit Dec 28 196? and confirmed by an electrocardiogram (*Fig 3 A*) P P 1 00 sec R R 1 64 sec and QRS 0 10 sec with Q wave in Leads 3 and aV_F as before but now for the first time with poor R wave *progression* through Lead V P had become more clearly notched in Lead 2 and diphasic in Lead V A similar record *April 8 1963* and a few episodes of giddiness led to the temporary use *of* prednisone up to 80 mg

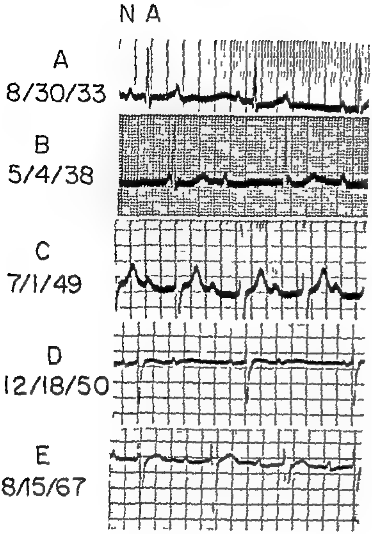

Fig 1 Case 1 NA Lead II in *A B* and *C* Lead V in *D* and *E* A V conduction appears in *C* and *E*

stated that he led a normal life without effort intolerance and denied any symptoms of faintness or of syncope Physical examination revealed an arterial pressure of 120/75 a normal cardiac size normal sounds and no murmurs or gallops An electrocardiogram (Fig 1 *E*) was unchanged from that of Nov 1964 Sinus rhythm was present with a rate of 80 per minute The P R interval was 0.36 to 0 40 sec the QRS interval was 0 09 sec Again an occasional P wave failed to evoke a ventricular response when its onset fell within 0 28 sec of the preceding QRS On this occasion he exercised vigorously for three minutes his heart rate rose to 130 per minute and remained regular Neither exercise nor carotid sinus stimulation altered the P R interval

On June 24 1970 an electrocardiogram recorded for Richard R Babb M D showed uniform conduction with a P R interval of 0 33 sec

Case 2 Marc Eckstein M D wrote as follows "KT age 72 was seen by me for the first time in 19›3 She was observed by another physician prior to my examination and was known to have had complete heart block for five years Her electrocardiogram revealed a pattern of complete heart block with a ventricular rate of 40 per minute QRS complex measured 0 09 sec and there was left axis deviation Patient did very well until Dec 1958 age 77 when she suddenly developed substernal pain dyspnea and orthopnea On hospital admission her electrocardiogram revealed the same pattern of complete heart block but ST segments were elevated Ventricular rate was 38 Sedimentation rate and enzymes were increased Patient was given Demerol oxygen and a mercurial and she was started on anticoagulants Since signs of congestive failure increased it was decided to digitalize her She received 2.5 mg of digoxin within 24 hours then 0 75 mg in the next 24 hours An electrocardiogram, taken after this 48-hour period revealed a regular sinus rhythm with a rate of 75 per minute PR interval was 0 18 sec and QRS 0 10 sec The axis remained the same but there were T wave changes, consistent with an acute process This rhythm persisted for two days then reverted to its original pattern when digoxin was stopped due to gastric complaints Patient recovered from this acute bout of myocardial infarction with congestive heart failure and lived until 1966 when at 85 she died during a Stokes Adams seizure Between 1958 and her demise she experienced several bouts of Stokes Adams seizures with documented runs of ventricular fibrillation interchanging with cardiac asystole but responded always to Isuprel and oxygen From 1961 she developed a right bundle branch block in addition to complete heart block which persisted to her demise in 1966 The ventricular rate remained around 38 and the QRS complex measured 0 12 sec "

Case 3 Sidney P Schwartz M D wrote as follows "HB aged 79 was known to have complete heart block for seven years before she was operated upon for carcinoma of the vagina. Shortly after operation she developed normal sinus rhythm (P R 0 20 sec) which was present when she died at 86 She represents the only patient out of a series of upward of 500 patients with all forms of heart block in whom an established type of complete heart block reverted to sinus rhythm without any medication "

Case 4 CW (No 08 58 80) was 63 in 1960 when a single episode of syncope led to the discovery of complete A V block documented by electrocardiograms recorded Sept 29 1960 (Fig 2 *A*) and Oct 6 1960 (P P 1 04 sec R R 1 6 to 1 8 sec QRS 0 12 sec left axis deviation and a pattern of right bundle branch block) On Oct 3 1961 an electrocardiogram showed 2 1 A V block without other change both before and after mild exercise (P P 0 78 to 0 62 R R 1 56 to 1 24 sec respectively and P R 0 32 sec)

Past history included diphtheria without recognized complications in childhood diabetes mellitus duodenal peptic ulcer and one paroxysm of tachycardia about 1942

No further episodes of syncope occurred until early in 1962 when there were a series of them for which he was seen by Thomas P Lyon M D on April 18 1962 He appeared healthy and was without detectable abnormalities other than cardiovascular ones The ventricular rate was 32 per minute rhythm regular but for a few premature beats the first sound varied in amplitude there was a moderate blowing apical systolic murmur and atrial sounds were present in diastole Arterial pressure was 235/100 mm Hg at first later 150 to 180/70 to 75

An electrocardiogram of March 6 1962 showed complete A V block (P P 1 0 sec R R 2 2 sec QRS 0 12 sec) with occasional ventricular premature beats but no other change since the earlier ones Electrocardiograms of May 18 and 25 and Oct 22 1962 (Fig 2 *B*) revealed the same rhythm and comparable rates however most ventricular complexes showed right axis deviation rather than the previous left

Table I Remission or recovery in established high grade or complete heart block

Patient	Previous duration of A V block (years)	Restoration of A V conduction		
		Age at onset (years)	Duration	Nature
Lenègre et al.	43 76	76	4 years to death	P R 0 22 to 0 30 sec., no blocked cycles.
Gilchrist	4?	42	16 years continuing	P R 0.28 to 0 32 sec and 3 2 Wenckebach block at first P R 0.24 sec with no blocked cycles 10-16 years later (Oct 31 196? and Aug. 30 1973 personal communications from A. R. Gilchrist and R M Marquis)
Campbell, et al.	35-47	?5 42	12 19 years continuing	P R 0 3? to 0 48 sec., no blocked cycles.
Lenegre et al.	22 29	29	13 years continuing	P R 0.3? to 0 37 sec., no blocked cycles
Nadas and Fyler* Case 1 NA	20	20	5 months known then relapse unknown duration (18 mo to 15 yr) then 8 yrs. or more continuing.	P R 0 40 sec rare blocked cycle at first. Later P R 0 33 sec with no blocked cycles.
Case 2, KT	10	77	2 days only	P R 0 18 sec
Case 3 HB	7	?9	7 years to death	P R 0 18 sec
Case 4 CW	7	70	4 days or more plus transient competition 6 mo after pacemaker insertion Sudden death	P R 0 12 sec 2 1 A V block with deep inspiration
Campbell (Case 125)	6	64	Brief 2 occasions 1 yr apart	P R 0 23 sec no blocked cycles later 2 1 and 3 1 A V block (P R 0 40 and 0.26 sec)
Case 5 SK	4	8?	11 mo until relapse plus brief remission 2 yrs. earlier	P R 0 28 (0 20 to 0 32) sec)

*Details [illegible] vailable

remission was 0 22 sec the longest 0 48 sec Gilchrist s[1] patient had Wenckebach periods in early remission but not later and the P R interval decreased with time Of the other congenital cases in remission blocked cycles were recorded only in Case 1 Conduction time in the acquired group was 0 18 to 0 40 sec., with 2 1 and 3 1 A V block in two patients No delta waves appeared in any

The anatomic defect was A V nodal region fibrosis and calcification of the mitral fibrous anulus in Case 4 in whom the coronary arteries were patent and only moderately atherosclerotic Calcific lesions in the vicinity of the conduction system known earlier to be present even with block which is paroxysmal were not shown radiologically in any case but of course may have been present in fact as they were in Case 4 In the first patient of Lenègre and co workers[4] a remarkable fibroadipose lesion virtually encapsulated the A V node The patient of Campbell and Sutman[3] at one time was thought to have had a ventricular septal defect but this diagnosis was given up later Neither these observations nor those of others on the lesions of heart block as recently reviewed[16] seem at all helpful in understanding these remissions We have no evidence as to the cause of block in the other patients None had myxedema nor did any receive thyroid[17]

A V conduction sometimes returns after the production of complete A V block as a complication of open heart surgery for congenital defects. Such remissions are rare after four weeks but in exceptional instances may be delayed for as long as two years and possibly even four years[18, 19] Intermittent 2 1 and 3 1 A V conduction was recorded by Erlanger and Blackman[20] subsequent to the production of complete block in dog No 3 in their classic experiments In more acute experiments Biggs also noted recovery of A V conduction after a considerable time

Remission took place in Case 2 shortly after

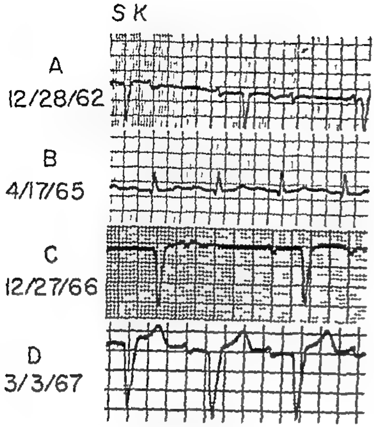

Fig 3 Case ■ SK Lead V in *A* *C* and *D* Lead II in *B* A V conduction appears in *B* and *D*

daily Complete heart block was present and the serum potassium was 4 1 mEq per liter when Dr Spiegl first saw the patient May 13 1963 Except as noted below the heart rate was 40 to 48 per minute at three dozen examinations from that date through Dec 27 1966 (Fig 3 *C*) during which period five unchanged electrocardiograms showed complete block

An electrocardiogram on Nov 10 1964 also showed complete block for the most part but ■ few cycles seemed to be conducted at a P R of 0 32 sec On April 17 1965 the heart rate was 73 per minute and an electrocardiogram revealed sinus rhythm with P R of 0 30 sec (Fig 3 *B*) There were rare cycles of 2 1 block ■ few supraventricular premature beats were conducted The heart rate was 42 per minute both two weeks before and two weeks after that record Similar bradycardia persisted during and following an operation for repair of a hiatal hernia July 28 1965 when gout appeared Diuretics with potassium replacement were used for mild edema through much of 1965 and 1966 the serum potassium was 4 7 mEq per liter on Nov 14 1966

On March 3 1967 the heart rate was 62 per minute and rates of 82 to 88 per minute were found in many subsequent examinations and electrocardiograms from that date (Fig 3 *D*) through Jan 1968 In these records the P R was usually 0 28 sec (0 20 to 0 32 sec) one atrial premature beat was blocked but many others were conducted for the first time left bundle branch block with left axis deviation appeared constantly on Aug 4 1967 and both were intermittent together a month later when normal ventricular complexes followed the pauses which succeeded ventricular premature beats But for the more rapid rates with sinus rhythm no other clinical changes were apparent However complete A V block asymptomatically returned on Feb 10 1968 and syncopal episodes late in 1968 led to the use of a transvenous demand pacemaker There was no A V conduction in any of 14 electrocardiograms recorded between Jan 20 1969 and Jan 23 1974 On the latter date both pacemaker and patient were functioning well [1]

Discussion

Salient points are set forth in Table I, in which the congenital cases are presented above, separately from those with acquired block, in each type, the cases are listed according to duration of complete block prior to remission Recovery has persisted for almost two decades each in the patients of Gilchrist[3] and Campbell[1 2] and for years in others with congenital block, remissions were much more brief in the acquired form, although one's duration was for seven years until death

Stokes Adams episodes were not observed in any of the congenital group, but did occur in Case 4 both before and at the onset of remission as well as in Cases 2 and 5 subsequent to remission

At its onset, acquired block often appears in paroxysms at first This does not seem to occur with congenital block and in general we have tried to avoid this problem by the arbitrary exclusion from consideration of remissions within four years of the establishment of block (although Case 5 may be an exception) But for a few cases described by Gilchrist[3] as following his Course A, with liability to recurrent syncopal attacks that phase in which paroxysms occur prior to the acquired establishment of complete block seems to be only two or three years [8 11 13]

Males and females are divided about equally Age at remission was from 20 to an extraordinary 76 years with congenital block 64 to 82 after four to ten years of acquired block In view of the usual age range within which acquired block is found it is not altogether surprising that remissions are more brief in this group than in those whose block ■ congenital Remission seems more frequent in the congenital variety especially in view of the fact that acquired block is more common than congenital block

All but Case 4 had narrow ventricular complexes during block, while patterns of defective intraventricular conduction continued in him and first appeared in three others with remission from acquired but not congenital block In the congenital group the shortest P R interval in

support from the absence of Stokes Adams syncope and the presence of narrow QRS complexes (and Wenckebach periods in one) during remission [8] All of the acquired block patients except Case 4 also had narrow complexes during high grade block but in this group the QRS was invariably widened during remission (no information available in Case 3) Stokes Adams episodes first appeared in two and Mobitz Type II was recorded in two patients this suggests that the site of block may have shifted distally in remission[33] in those with acquired disease

Summary

The return of A V conduction is described in a patient after two decades of high grade or complete congenital heart block Similar cases have been reported by others with remission or even recovery commencing up to the fourth decade or later A similar phenomenon is also described in four patients with acquired heart block of four to ten years duration in them remission was usually brief but persisted for seven years in one patient No full report of this seems to have been published previously Possible explanations are discussed but no conclusion is reached Apart from its interest the phenomenon is of importance with respect to the selection of demand type electronic pacemakers in the management of patients with heart block.

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myocardial infarction In Case 3 it occurred during a postoperative phase and in Case 1, the initial remission was related temporally to an Army pre induction examination These events, of course, suggest a consideration of endogenous adrenal corticosteroid release in stressful situations with consequent improvement in A V conduction It is difficult to understand how this could lead to prolonged remissions and in other patients remissions occurred in the apparent absence of unusual stress

The return of sinus rhythm in A V block has been reported to follow the use of isoproterenol hydrochloride prednisone chlorothiazide, or electronic pacemakers [2, 4] Prior to remission a trial of chlorothiazide had failed in Case 4 and one of prednisone had failed in Case 5 One must point out that many of the relevant case reports fail to note the prior duration of heart block available data strongly suggest that most, if not all of these patients were within two or rarely three, years of onset and thus might have been in the paroxysmal phase A pacemaker was inserted in our Case 4 for the paradoxical reason that episodes thought to be Stokes Adams ones recurred with his spontaneous remission relapse into complete block followed this operation but six months later A V conduction reappeared briefly, and a year later he died suddenly Considerations of this sort support the use of a demand pacemaker for the incidence of paroxysmal ventricular arrhythmias and the chance of death increase in the face of competition between endogenous and exogenous pacemakers We now use only the demand type of pacemaker [9, 12]

We have reviewed our own early cases of pacemaker insertion in order better to define any relationship between return of conduction and preoperative duration of complete block The results show that intermittent A V conduction is common following pacemaker implantation In the present series it was documented in 23 out of 91 cases (25 per cent) This compares with an incidence of temporary return to sinus rhythm of 20 to 23 per cent in other reports [7, 9] In our series sinus rhythm was present in four cases at the time of pacemaker insertion, was the dominant rhythm with occasional episodes of sinus arrest and slow idioventricular rhythm in two instances, and in another was present except during anginal attacks when heart block developed This last patient demonstrated continuous sinus pacemaker competition and died suddenly three months following pacemaker insertion without evidence of recent infarction

The remaining 19 case histories were examined to determine if postoperative sinus pacemaker competition in fact represented remission of established heart block following the institution of cardiac pacing The longest interval between the onset of heart block and pacemaker insertion in these patients was 27 months with an average interval of 10 months except Case 4 described above Thus, 18 of the 19 patients who demonstrated occasional A V conduction postoperatively may be considered to have been in the paroxysmal phase of complete heart block Indeed, 10 of the 19 patients showed A V conduction immediately prior to or at the time of pacemaker insertion None of the patients with a history of complete heart block longer than two years developed A V conduction postoperatively (except Case 4, above) These considerations fail to support the thesis that cardiac pacing *per se* promotes the return of sinus rhythm in established heart block

Controversy has attended the existence of two particular types of conduction A V conduction within a supernormal phase and A V retrograde conduction, in patients with high grade or otherwise complete A V block [33, 34] We detected the latter in none of our patients while the former was recorded occasionally only in Case 1

Finally we have considered the possibility that remission may depend upon the establishment of accessory pathways Accelerated A V conduction has been reported as appearing in association with myocardial infarction and other insults [35] Our patients however lacked delta waves and none had P R intervals shorter than 0 18 sec so that this hypothesis lacks support

Although His bundle studies were not obtained in any of the patients discussed here results of such studies in others may be relevant In congenital block without associated cardiac disease block is almost invariably proximal to the bundle of His [36, 38] In acquired high grade or complete A V block with narrow ventricular complexes it usually is proximal, with wide ones distal [3] Therefore it would appear that in all of the congenital cases presented here the block should have been proximal a speculation receiving some

Review

Arterial thromboembolic complications in patients with Starr-Edwards aortic ball valve prostheses

Jon Dale M D
Oslo Norway

Arterial thromboembolic complications occur frequently in patients with implanted hearts valves[1 4] systemic emboli representing a considerable threat in the early and late course of valve replacement[2 9] since the emboli often lodge in cerebral arteries[7 10 12] All patients probably run the same risk of such complications regardless of cardiovascular success of the operation

Anticoagulant treatment has been widely used in order to reduce arterial thromboembolism but full protection has not been achieved[1 3 9 11 4] For the same purpose the older Starr Edwards aortic ball valves were modified[5] and a reduced incidence has been found with the cloth covered valves.[4] More recently disc valves have been introduced but although a low rate of thromboembolic episodes has been found in a series of patients with aortic valves of this type[8] a higher incidence has been reported with mitral disc valves and arterial thromboembolism still constitutes a serious problem in valve replacement

The present investigation was performed in order to reveal the incidence of arterial thromboembolic complications in patients with Starr Edwards aortic ball valves and to study factors that might influence the incidence Such evaluation was necessary since the patients entered a clinical trial with acetylsalicylic acid to study its antithrombotic effects Further a comparison with results from a similar study in patients with disc valves will be made later

Material and methods

Single Starr Edwards aortic ball valves were implanted in 253 patients from January 1967 until December 1970 During the first year some valves of other types were also used but for the rest of the period only Starr Edwards valves were inserted Until November, 1968 80 prostheses of series 1200 with Silastic balls and metal cages were implanted from then on 173 valves of series 2300 with hollow stellite balls and cloth covered cages[1] were used The operation was performed in 181 men and 72 women the mean age being 52 2 and the range 20 to 71 years No patient was regarded to be too ill for operation and 18 of the valve replacements were done as emergency operations because of advanced circulatory failure

Valve implantations were only done in this hospital in Norway during those years which explains the large number of patients included in the study All operations were performed by the same experienced team of surgeons and the operating technique and postoperative care remained largely unchanged Oxygenation was achieved by a Rygg Kyvsgaard bubble oxygenator and since 1970 a Kay Anderson disc oxygenator has been employed Light hypothermia 32 to 34° C was routinely used and the left coronary artery was always perfused The patient was heparinized with 300 I U of heparin per kilogram of body weight and after operation the activity was neutralized by protamine Oral anticoagulation with Dicumarol or warfarin was started after two to four days unless bleeding persisted

Follow up

Most of the patients have been sent to the cardiologic department one or more times after operation and their hospital records were examined Reports have been obtained concerning patients who died in other hospitals or at home

All surviving patients were asked to meet for examination in the autumn of 1972 and all except six were able to come The examination included

From the Institute for Thrombosis Research University Hospital, Rikshospitalet Oslo Norway

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Reprint requests to Jon Dale M D Institute for Thrombosis Research, University Hospital Rikshospitalet, Oslo 1 Norway

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thrombotic masses interfered with the movement of the ball and the valve was replaced by another one

The average observation time for the 216 patients that survived the postoperative period was 36.5 months as calculated from the beginning of the second month (Table III) Thus a total of 7896 patient months were recorded Late thromboembolic complications were found to be responsible for 7 of the 41 deaths that occurred during the follow up period

A total of 46 late thromboembolic episodes were recorded in 40 patients the majority of these suffering from cerebral emboli causing four deaths (Table IV) Autopsy was done in three patients emboli were demonstrated in cerebral arteries in two of them while a cerebral infarction was found in the third Two other embolic episodes caused severe permanent disability Five patients suffered a myocardial infarction and three died Autopsy was performed in two and thrombi were found in moderately atherosclerotic coronary arteries of both Thus late arterial thromboembolic complications were observed in 18.5 per cent of the patients during the follow up period causing 17 per cent of the deaths The incidence of the late complications was 7.0 episodes per 100 patients per year

Autopsy was done in 69 of the 78 patients who died and a thrombus was found on the ring or cage of the valve in 5 cases after two early and three late deaths One of the patients had died two weeks after operation from a myocardial infarction caused by extension of the thrombus as mentioned and another from a cerebral embolus after six months both had valves of series 2300 No embolic episodes were revealed in the other three patients who died from complications unrelated thrombosis and had valves of the older type

The incidence of late thromboembolic complications was considerably higher in the patients with valves of model 1200 than in those with the newer valves (Table V) the difference being highly significant ($p < 0.01$) The mean observation time differed however between the two groups Therefore the incidences recorded during the first two years after the operations were compared this difference also being significant ($p = 0.01$)

Table III Observation time in patients with Starr Edwards aortic ball valves The first post operative month is not included

Starr Edwards valve series	*No of patients*	*Mean observation time (months)*
1200	70	44.7
2300	146	32.7
Total	216	36.5

Table IV Late thromboembolic complications in patients with Starr Edwards aortic ball valve prostheses

Thromboembolic complication	*No of complications*	*No of patients*	*No of deaths*
Cerebral emboli	33	28	4
Serious	7		
Intermediate	14		
Mild	12		
Peripheral emboli	7	6	
Myocardial infarction	6	6	3
Total	46	40	7

The long observation period in many of the patients made it possible to study thromboembolism in relation to time after operation (Tables V and VI) Thus 3 502 patient months were observed after more than two years The episodes recorded were quite equally distributed throughout the observation period A slight nonsignificant reduction was found in patients with valves of series 1200 after two years This contributed to keep the total incidence quite constant since the number of patients with the less thrombogenic valves of the newer series fell gradually in time and none of them were followed for more than four years

An attempt was made to estimate whether the anticoagulant treatment was satisfactory at the time of thromboembolic complications The Thrombotest (TT) values had been determined less than two weeks before 35 of the 46 episodes (Table VII) and 80 per cent of the values lay within the therapeutic range of 5 to 15 per cent activity This compares favorably with TT levels at the end of the follow up when 67 per cent of the 169 values were satisfactory Although the

Table I Mortality after implantation of single Starr Edwards aortic ball valve prostheses

	Number of patients		
		With valves of series	
	Total	1200	2300
Valve implantations	253	80	173
Early deaths	37	10	27
Alive after one month	216	70	146
Late deaths	41	18	23
Alive at follow up	*175*	*52*	*123*

Table II Postoperative thromboembolic complications in patients with Starr Edwards aortic ball valve prostheses

Type of thromboembolic complication	No of complications	No of patients	No of deaths
Cerebral emboli (total)	5	4	
A Serious	4		
B Intermediate	1		
C Mild	0		
Peripheral emboli	1	1	
Myocardial infarction	6	6	6
Thrombus on valve leakage	2	1	
Total	14	12	6

a careful history of thromboembolic or bleeding episodes a physical examination, roentgenological examination of heart and lungs and blood tests regarding platelet function coagulation fibrinolysis intravascular hemolysis, and anemia Some of the results will be published separately

Anticoagulant treatment was controlled by Thrombotest,[19] reflecting the activities of coagulation factors II VII and X, aiming at a therapeutic level between 5 and 15 per cent

In addition a form was sent to the doctors of all patients asking for information Thus the data presented are collected in three different ways From hospital records examination of the patients and information from their doctors None of the patients were lost for follow up

Embolic episodes were listed if the following criteria were fulfilled (1) Acute onset with full development of symptoms in the course of 20 minutes (2) Disturbance of neurological function in cerebral embolism, or functional disturbance due to arrested blood flow to other regions (3) Observation of the symptoms by others than the patient, and (4) Duration of symptoms for more than 30 minutes The diagnosis of myocardial infarction was based on generally accepted criteria history of acute precordial pain electrocardiographic signs, and rise of temperature, leukocyte count or transaminases Alternatively the diagnosis of arterial thromboembolism could be made when a thrombus was demonstrated at autopsy or at operation

Cerebral emboli were divided in three subgroups according to the severity 'Serious were emboli causing death or considerable permanent disturbance of neurological function, intermediate emboli producing more moderate disability lasting for at least two weeks and mild' were episodes with slight and transient symptoms

Results

The mortality rate at operation and during the first postoperative month was 14 6 per cent (Table I) and this remained constant throughout the period The postoperative thromboembolic complications are listed in Table II Five cerebral embolic episodes occurred, four led to permanent disability but none of them were fatal Seven myocardial infarctions were diagnosed all patients died and autopsy was performed in six Thrombi were found in coronary arteries in five of them one thrombus extended from the ring of the implanted valve into the left coronary artery Coronary atherosclerosis was extensive in one more moderate in two and minimal in the three other patients A myocardial infarction was found in spite of open coronary arteries in a 40 year old man who died after several days of intractable shock This case is therefore not recorded as thromboembolic Three cerebral embolic episodes and three myocardial infarctions occurred within the first week

Thrombosis formation might also disturb the function of the valve itself A 36 year old man developed leakage of the prosthetic valve three weeks after the implantation At reoperation thrombotic material limiting the movement of the ball, was removed from the cage of the valve Two weeks later the symptoms reappeared and a third operation was performed Newly formed

cleared from plasma.[31] As a consequence of these changes thrombus formation may start immediately or shortly after the operation explaining why valve thrombi are found and emboli occur[3, 6] within the first week.

The high incidence of early myocardial infarction[1] may have several causes. Emboli from the valves may cause infarction and coronary thrombi may be formed because of interference with the intima at operation or at cannulation or to disturbance at coronary blood flow during extracorporeal circulation[3] or after the implantation. However, traumatic lesions were found in only one of the patients who died from early infarction.

The incidence of late arterial thromboembolic complications in patients with aortic ball valves receiving anticoagulant treatment varies considerably from one investigation to another.[3, 6, 5, 3] This may partly be explained by differences in observation time, valve type, diagnostic criteria, registration manner, or intensity of anticoagulant treatment, and most materials have been too small to allow estimation of the incidence. In three studies the annual rate of complications compared well with the results presented here.[1] Most of the late thromboembolic episodes were cerebral, which may reflect the real distribution, but it is more likely that small emboli in other organs are asymptomatic and therefore remain unrecognized.

The diagnosis of cerebral embolism was based on strict criteria. A sudden onset was demanded in order to exclude cases of intracerebral hemorrhage since studies on general autopsy materials have shown that thrombotic or embolic arterial occlusions are the predominant causes of larger[33] and smaller[34] cerebral infarcts. Definite disturbance of neurological function was regarded to be necessary to exclude episodes unrelated to thromboembolism. Nevertheless, a risk of erroneous diagnosis still exists, especially for the milder episodes. On the contrary, the incidence of cerebral embolic episodes may be higher than recorded, since five cases of sudden death, usually believed to be due to ventricular fibrillation or cardiac standstill, were not included. Small cerebral emboli may also remain undetected and the strict criteria may lead to exclusion of episodes with less typical symptomatology. Late myocardial infarction was regarded as a thromboembolic complication, although the etiology may be complex.[22] However, the rate of thrombotic or embolic infarctions might be underestimated since smaller infarctions with moderate symptoms could be unrecognized.

The ring and cage of the prosthesis of model 2300 was covered with cloth in order to favor endothelialization and thereby reduce thromboembolism.[15, 37] A neointima is formed, but not always completely, and thrombotic material may be found instead.[3] A somewhat lower incidence of arterial thromboembolism with cloth-covered than with uncovered valves has been reported,[6, 7] and the number of embolic episodes has been found to decline after 6 to 12 months[6, 21] when endothelialization should have taken place. In the material presented here the incidence was significantly lower in patients with valves of series 2300 than of series 1200, but the rate was not reduced after one or two years. Since model 2300 has a double cloth covering of the ring, the orifice to ball ratio is smaller than in model 1200,[3] and the systolic gradients across the valves are considerably higher.[4, 21] Consequently, more turbulent flow is probably caused by these valves and the degree of hemolysis is higher.[3] In spite of this, the tendency of thromboembolism was reduced, which may be due to endothelialization of the cloth. The cloth-covered prosthesis has been developed further to the composite seat types with a greater orifice to ball ratio and better hemodynamic performance[3] and probably a lowered risk of embolic episodes than with type 2300,[23] although thrombi are known to be formed.[1] Composite seat valves have not been used in this hospital since the disc valves became available.

It has been claimed that the tendency to arterial thromboembolic complications is reduced after two years. In the material presented here the observation period is long enough to consider the influence of time upon the occurrence of such complications. The incidence was quite constant from year to year after operation. The longer the observation time, the higher was the percentage of patients with the older, more thrombogenic valve 1200. This might of course tend to hide a slightly decreasing tendency for thromboembolism. Nevertheless, a striking lowering of the incidence with time did not occur.

Since early studies revealed a reduced incidence of arterial embolic episodes in ball valve patients

Table V Late thromboembolic episodes in patients with Starr Edwards aortic ball valve prostheses Relation to valve type and time after operation

	Starr Edwards aortic prostheses		
	Series 2300	*Series 1200*	*Total*
No of thromboembolic			
episodes	17	29	46
Within two years	10	15	25
After two years	7	14	21
Episodes per 100			
patients per year	4 3	11 1	7 0
Within two years	4 0	13 2	6 8
After two years	4 8	9 5	7 2

Table VII Distribution of Thrombotest (TT) values before 35 of the 46 late thromboembolic episodes and at the end of the follow up period in 169 patients with aortic ball valves

	Distribution of TT values in per cent	
TT value	*Before episode*	*At end of follow up*
Lower than 5 per cent	0	1 2
5 to 10 per cent	34 3	36 3
11 to 15 per cent	45 7	30 4
16 to 20 per cent	14 3	12 6
21 to 25 per cent	2 9	8 2
Higher than 26 per cent	2 9	11 1

Table VI Number of late thromboembolic episodes and calculated incidence for each year after valve implantation

Time after operation	*No of episodes*	*Episodes per 100 patients per year*
Within the first year*	13	7 1
One to two years	12	6 6
Two to three years	11	7 7
After three years	*10*	6 7

*Only episodes observed during the last 11 months of the first year are included

activity of coagulation factors could not be established at the time of thrombus formation the anticoagulant therapy was well controlled in most of the patients

Some degree of affection of the mitral valve was found in 25 9 per cent of the patients who had a single aortic valve implanted and in some of them a mitral commisurotomy had been performed Thromboembolism did not develop more frequently in the patients with concomitant mitral disease than in the others

Continuous arrhythmia mostly atrial fibrillation, was seen in 29 6 per cent of the patients, but was not found to be a predisposing factor for late arterial thromboembolism

There was no relation between the incidence of late thromboembolic complications and the heart size in patients who survived the first postoperative month Thus the mean preoperative heart size in patients who developed late episodes was 672 ml per sq M as compared to 674 in those who did not, while the mean values in the two groups at the end of the follow up period were 573 and 589 ml, respectively The plasma lactate dehydrogenase activity (LDH) reflecting the degree of intravascular hemolysis[20] was compared in patients with and without late thromboembolic episodes The LDH values were insignificantly higher in patients without late complications in both valve groups

Discussion

The early incidence of thromboembolic complications following valve implantation is high[1, 2, 4, 8, 10, 11] and myocardial infarction is a frequent cause of early death[1, 2, 8, 21, 22] Arterial thrombi are mainly composed of platelets and fibrin[23, 24] and platelet aggregation and adhesion to subendothelial structures or foreign surface are early steps in thrombus formation[25, 27] Thus the foreign material represented by the valve itself and the turbulence caused by the passage of blood through it will favor thrombosis, and thrombi are often found on the cage of the valve[1, 8, 14, 21] as demonstrated in six of our patients After a period of thrombocytopenia following heart operations, thrombocytosis develops with hyperreactive platelets[28] which may in part explain the strong tendency to arterial thrombosis Since intravascular hemolysis occurs in almost all patients with aortic ball valves[29] the platelet aggregating substance adenosine diphosphate (ADP)[30] might be liberated in amounts great enough to influence platelet behavior near the valve even if ADP is rapidly

cleared from plasma.[11] As a consequence of these changes thrombus formation may start immediately or shortly after the operation, explaining why valve thrombi are found and emboli occur[3, 6] within the first week.

The high incidence of early myocardial infarction[1, 2] may have several causes. Emboli from the valves may cause infarction, and coronary thrombi may be formed because of interference with the intima at operation or at cannulation, or to disturbance at coronary blood flow during extracorporeal circulation[11] or after the implantation. However, traumatic lesions were found in only one of the patients who died from early infarction.

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The diagnosis of cerebral embolism was based on strict criteria. A sudden onset was demanded in order to exclude cases of intracerebral hemorrhage, since studies on general autopsy materials have shown that thrombotic or embolic arterial occlusions are the predominant causes of larger[3] and smaller cerebral infarcts. Definite disturbance of neurological function was regarded to be necessary to exclude episodes unrelated to thromboembolism. Nevertheless, a risk of erroneous diagnosis still exists, especially for the milder episodes. On the contrary, the incidence of cerebral embolic episodes may be higher than recorded, since five cases of sudden death, usually believed to be due to ventricular fibrillation or cardiac standstill, were not included. Small cerebral emboli may also remain undetected, and the strict criteria may lead to exclusion of episodes with less typical symptomatology. Late myocardial infarction was regarded as a thromboembolic complication, although the etiology may be complex.[22] However, the rate of thrombotic or embolic infarctions might be underestimated, since smaller infarctions with moderate symptoms could be unrecognized.

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It has been claimed that the tendency to arterial thromboembolic complications is reduced after two years.[7] In the material presented here the observation period is long enough to consider the influence of time upon the occurrence of such complications. The incidence was quite constant from year to year after operation. The longer the observation time, the higher was the percentage of patients with the older, more thrombogenic valve 1200. This might of course tend to hide a slightly decreasing tendency for thromboembolism. Nevertheless, a striking lowering of the incidence with time did not occur.

Since early studies revealed a reduced incidence of arterial embolic episodes in ball valve patients

receiving anticoagulants[11, 39] such treatment has been widely used Some authors have reported a lower rate of emboli in patients with well controlled anticoagulant therapy than in those with greater fluctuations in the activity of coagulation factors[7, 1] In the present study, the majority of TT values lay within the therapeutic range before the episodes and the TT levels were quite constant in most of them, indicating that thrombosis formation started in spite of adequate treatment Thus well performed anticoagulant therapy does not entirely prevent arterial thromboembolism This is not surprising since adhesion and aggregation of platelets are early steps in arterial thrombosis formation and the platelets remain unaffected by anticoagulants Drugs that modify platelet functions might theoretically have antithrombotic effects and the patients therefore entered a controlled clinical study with acetylsalicylic acid Sullivan and colleagues[40] found a significantly reduced incidence of arterial thromboembolism in patients receiving dipyridamole

The lack of correlation between continuous arrhythmia and thromboembolic episodes is in accordance with the findings of others[7, 8, 11, 31] However the possible effects of intermittent arrhythmia cannot be excluded Concomitant mitral valve disease might increase the risk of emboli but such a relation was not found The equally low incidence of late thromboembolism in patients with arrhythmia or mitral disease as in the others could be ascribed to the anticoagulant treatment

The rate of late thromboembolic episodes could be inversely related to the cardiocirculatory success of the valve replacement However, the mean heart size did not differ between the patients who developed such complications and the others, indicating that a successful operation does not lower the risk of thromboembolism Substances that could induce platelet aggregation and coagulation are liberated from red cells during intravascular hemolysis[1] The degree of hemolysis was however unrelated to the incidence of arterial thromboembolic complications

Summary

Arterial thromboembolic complications were studied in 253 patients who had a single aortic Starr Edwards ball valve implanted During the first postoperative month six patients died from myocardial infarction, one was reoperated because of leakage caused by thrombus on the valve, and five others suffered six thromboembolic episodes

Forty six late thromboembolic complications occurred in 40 of the 216 patients who survived the postoperative period Seven died four from cerebral emboli and three from myocardial infarction The late incidence was 7 episodes per 100 patients per year Valves of series 1200 carried a significantly higher risk of arterial thromboembolism than did those of series 2300, and most episodes occurred in patients with well controlled anticoagulant treatment The incidence was not influenced by time since operation continuous arrhythmia concomitant mitral valve disease heart size or the degree of intravascular hemolysis

It is concluded that arterial thromboembolic complications represent a major threat to patients with aortic ball valves even several years after operation and in spite of intense anticoagulant therapy

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Fundamentals of clinical cardiology

Clinical uses of His bundle electrocardiography Part II

Masood Akhtar, M D
Anthony N Damato, M D
Antonio R Caracta, M D
Staten Island N Y

Supraventricular vs ventricular arrhythmias

The origin of single or multiple beats with wide and bizarre QRS complexes may at times be difficult to determine from the surface ECG alone (Fig 1) This is especially true in atrial fibrillation where there is absence of discrete P waves (Fig 2) HBE recordings have proved useful in making the distinction between beats of supraventricular and ventricular origin [1,2] In the former (i e arising from the bundle of His or above) bundle of His deflections precede the QRS complex by a normal or longer than normal H V interval (Figs 1 and 2) For beats arising more distally (i e, bundle branches or the Purkinje network) the inscription of the His bundle potential either occurs within the ventricular electrogram (Fig 1) or precedes it by a value significantly less than normal

The ECG distinction between ventricular tachycardia (VT) and supraventricular tachycardia (SVT) with aberration depends primarily on analysis of (1) the rate and regularity of the arrhythmia (2) the QRS morphology (3) presence or absence of P waves (4) the relationship of P waves to QRS complexes and (5) the presence of fusion beats The occurrence of normal or fusion QRS complexes during a tachycardia with wide QRS complexes is considered the hallmark for the ECG diagnosis of VT There are at least three mechanisms responsible for normal or fusion beats occurring during a VT (1) dissociated sinus capture beats, (2) retrograde A V nodal re entry with ventricular echo beats and (3) premature ventricular beats originating from the contralateral ventricle Even though fusion or normal QRS complexes occurring during an episode of tachycardia with wide QRS suggests a ventricular origin of the arrhythmia such beats are occasionally seen in SVT with aberrant conduction to the ventricles Intermittent normalization of the QRS complex during an SVT with aberrant ventricular conduction may occur under the following settings (1) When Wenckebach phenomenon occurs in a bundle branch displaying the block pattern on the surface ECG[3] The successive supraventricular impulses may block more proximally and finally the impulse does not penetrate the bundle branch The nonpenetration of the bundle branch results in a longer recovery time and the next supraventricular impulse may have normal intraventricular conduction following which the cycle is repeated It should be pointed out that partial penetration with ineffective propagation or non penetration of the bundle branch will result in similar QRS complexes and the latter is reflected on the ECG as periodic QRS normalization during a tachycardia with wide QRS complexes (2) When during an SVT with aberrant ventricular conduction ectopic impulse formation occurs in the refractory bundle branch distal to the site of block If ipsilateral ventricular activation from the ectopic impulse coincides with activation of the contralateral ventricle from the supraventricular impulse complete normalization of the QRS complex may be observed Asynchronous activation of the two ventricles by the two impulses may result in different degrees and types of fusion activation

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Reprint requests Masood Akhtar M D Cardiopulmonary Laboratory United States Public Health Service Hospital Staten Island N Y 10304

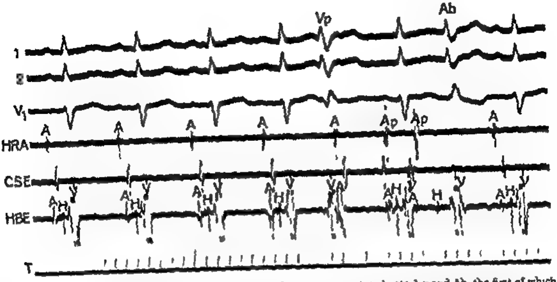

Fig 1 Ventricular and supraventricular beats Illustrated are two premature beats Vp and Ab the first of which (Vp) represents a beat of ventricular origin the His bundle electrogram is obscured by the ventricular electrogram The beat of supraventricular origin (Ab) is preceded by a His bundle deflection with H V interval which is greater than normal.

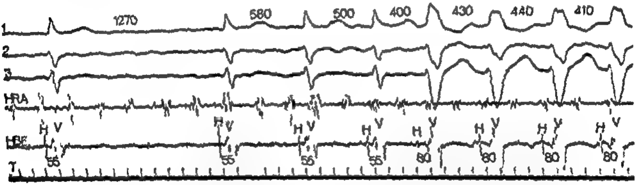

Fig 2 Atrial fibrillation with aberrant conduction of LBBB (last four QRS complexes) which could be misinterpreted as a ventricular tachycardia since according to the general rule of aberration the third QRS complex (short cycle following a long cycle) would be expected to be aberrant. Since aberration occurs at cycle lengths < 500 msec this probably represents a rate related phenomenon

Generally the bundle of His during *ventricular tachycardia* is activated retrogradely and its inscription is obscured by the ventricular electrogram Occasionally however the retrograde His bundle deflection may precede the QRS complex during a ventricular tachycardia thereby giving the erroneous impression *that the arrhythmia* is of supraventricular origin In these instances the H V intervals are significantly shorter than those recorded during ventricular activation by supraventricular impulses

It is important that the His bundle potential is carefully looked for during normal or fusion ventricular beats when studying a suspected ventricular tachycardia *If spontaneous* supraventricular beats are not observed termination of the arrhythmia may be *attempted* with atrial pacing or with therapeutic agents like procainamide

The clinical usefulness of HBE in making a more definitive diagnosis of VT is exemplified by the recent demonstration that bidirectional tachycardia may be of ventricular or supraventricular origin the former being more common in cases documented by HBE[43] During bidirectional tachycardia the QRS complexes usually

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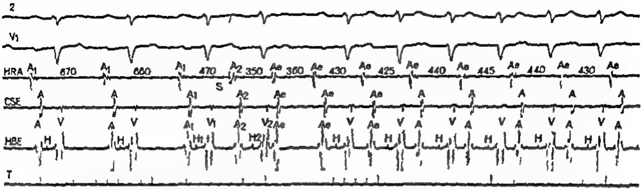

Fig 4 Supraventricular tachycardia (sinus node re-entry) During sinus rhythm (A) a premature beat (A_2) initiates a SVT (sinus node re-entry) with a high to low atrial activation sequence similar to sinus beats. It is to be noted that the first beat of SVT (Ae) blocks proximal to the bundle of His, which also argues against A V nodal re-entry being the mechanism of this type of tachycardia

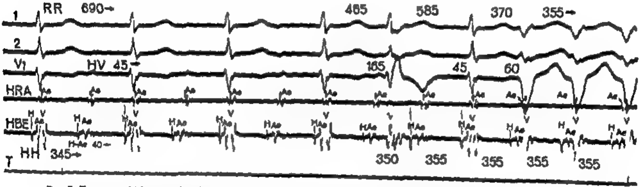

Fig 5 Functional block in the HPS during a complex SVT The tracing (taken from the same patient as shown in Fig 3) shows an episode of SVT during which a functional 2 1 block within the HPS developed following a long short cycle sequence (not shown) Note the low to high atrial activation sequence (Ae) during the SVT and that the H Ae interval remains constant during the block, indicating that ventricular muscle was not an essential link in the re entrant circuit The tracing also shows the mode of termination of the 2 1 block below the bundle of His The fifth QRS complex shows a RBBB aberration with an H V interval of 165 msec. during 3 2 Wenckebach type of conduction within the HPS after which 1 1 A V conduction resumes with ventricular aberration The usefulness of His bundle electrogram recordings in this complex arrhythmia is obvious.

propagate to the bundle of His Re entrant tachycardias (with a low to high sequence of atrial activation) which are initiated by a premature atrial beat which antegradely blocks within the HPS (i e no ventricular response) favors A V nodal re entry (Fig 5) and excludes re entry via a muscle to muscle bypass tract of the Kent type

Even though re entry in the A V and sinoatrial nodes are relatively well documented entities there is no doubt that a significant number of atrial tachycardias are due to atrial ectopy or intra atrial reentry

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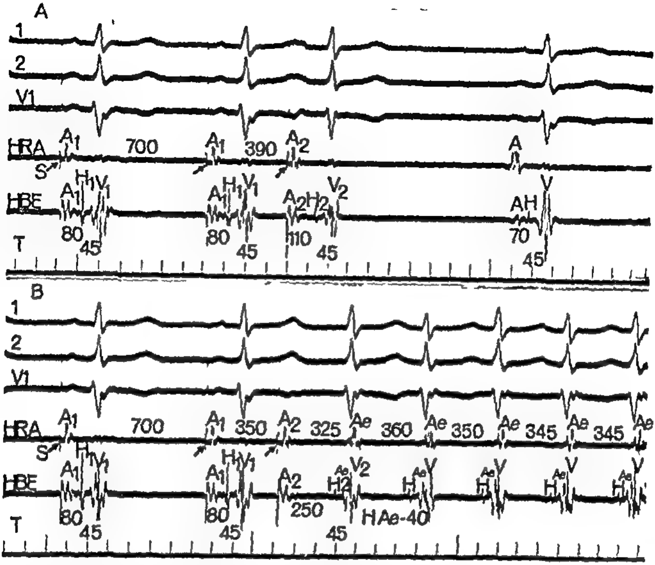

Fig 3 Supraventricular tachycardia (A V nodal re entry) In panel *A* a premature atrial beat (A_2) is coupled to *the preceding basic drive beat (A) at a coupling interval of 390 msec A conducts with an A H_2 of 110 msec after* which sinus rhythm follows At a closer A A interval of 350 msec (panel *B*) A_2 conducts with a longer A H_2 interval of 250 msec and a sustained SVT is initiated Note the low to high sequence of atrial activation during the SVT as compared to the high to low sequence during sinus rhythm (panel *A*) Note also that the low atrial activation precedes ventricular activation (H Ae < H V) and the P wave polarity is difficult to determine from the surface ECG

display fixed right bundle branch block pattern and alternating left and right axis deviation [8]

Paroxysmal atrial tachycardia

It has been demonstrated that paroxysmal atrial tachycardia may result from re entry occurring in either the sinus or A V nodes [10 14] Both types of tachycardia may be abruptly initiated by a single properly timed premature atrial beat occurring within the relative refractory period (RRP) of either node (Figs 3 and 4) A V nodal re entry is seen more frequently than sinus nodal re entry In the former the sequence of atrial activation is from the low to high atrium and the P waves although inverted in Leads II III and aV_F, are frequently obscured by the QRS complex or S T segment (Fig 3) In sinus nodal re entry the sequence of atrial activation is from the high to low right atrium and the P waves which precede the QRS complexes are very similar to those of sinus rhythm Both types of re entrant nodal tachycardias may be abruptly terminated by (1) carotid sinus pressure (as well as other vagal maneuvers) or (2) a properly timed premature atrial depolarization

Sinus nodal re-entry can be initiated by premature atrial beats which block in the A V node whereas A V nodal re entrant paroxysmal supraventricular tachycardias rarely if ever result from premature atrial beats which fail to

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

Clinical value of plasma renin determinations in renovascular and primary hypertension

Lot B. Page, M.D.
Boston, Mass.

The general availability of plasma renin determinations in the past few years has raised hopes of improving accuracy in the detection of patients with secondary forms of hypertension, improving selection of patients for renovascular surgery, and in classifying patients with primary hypertension in new ways.

The physiology of the renin-angiotensin system has recently been reviewed. The clinical value of plasma renin determinations is still surrounded by controversy. The detection of low values and especially the failure of plasma renin activity to rise in response to stimulation is of recognized value as a screening test for primary hyperaldosteronism. Wide use of renin determinations has disclosed that a large number of hypertensive patients who do not have primary hyperaldosteronism have suppressed responses ("low renin hypertension").

Conflicting claims have been made concerning the value of renin determinations in the detection and selection for surgery of patients with renovascular hypertension, and also concerning the usefulness of classifying patients with primary ("essential") hypertension as "high," "normal," or "low" renin forms of hypertension.

Selection of patients for renovascular surgery

Over a period of many years, the problem of accurately selecting patients for surgical treatment of renovascular hypertension has continued to engage the attention of investigators and clinicians alike. There have been repeated surges of enthusiasm as new physiological measurements, new surgical techniques, and new levels of understanding of the role of the kidney in hypertension have been reached. Since long term postoperative follow up is necessary to assess the adequacy of the selection process, disillusionment with the results of surgery has often been overlapped with renewed enthusiasm for yet another refinement in the selection process. In the mid 1970's the imperfections of the selection techniques of ten years ago are apparent. Nevertheless, there seems to be reason for cautious optimism based on improved understanding of the pathophysiology of hypertension and substantially better ways of assessing the relative roles of the renin-angiotensin system, sodium metabolism, and other factors in hypertensive patients.

Evaluations of results of surgery

Investigators reporting results of surgery have generally agreed in defining a "cure" as a reduction in blood pressure to 140/90 or less without medication a year or more after surgery. Invariably an "improved" category has also been included. This has been defined more variously. These are patients who remain hypertensive but are either more readily controlled on smaller doses of antihypertensive medication, or show a defined reduction in blood pressure in comparison with preoperative values. Almost all series lump together the cured and improved patients as those who have "benefited from surgery." In patients with severe hypertension which has been refractory to medical therapy, there is certainly justification for a surgical procedure which facilitates good control on a simple regimen. On the other hand, patients with renovascular hypertension are generally not more resistant to medical therapy than patients with primary hypertension of equivalent severity.[2,3] "Cure" and "improvement" are entirely different endpoints and should be kept separate in the clinician's mind. A reduction in the daily dose of medication may be

From the Department of Medicine, Newton Wellesley Hospital, Newton Lower Falls, Mass., and Tufts University School of Medicine, Boston, Mass.

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Reprint requests: Lot B. Page, M.D., 2000 Washington St., Newton Lower Falls, Mass. 02162.

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nation These variables have often been poorly controlled in the past and this may account for much of the past disappointment in clinical usefulness of renin determinations Better control of these variables use of more standardized methodology and of a new class of agents the competitive angiotensin inhibitors has already given promise of considerably increased accuracy in diagnosis of remediable renovascular disease The critical test is always prolonged follow up of cases selected for surgery and this will require more time

Methodology of plasma renin determinations

Technical details of methodology need not concern the clinician Nevertheless knowledge of the accuracy reproducibility and sources of error in methods are essential in interpreting results in the clinical setting Until the late 1960s plasma renin determinations were based on a variety of bioassays available only in a small number of research laboratories Radioimmunoassay for angiotensin II was first developed in 1967[1] and later similar radioimmunoassays for angiotensin I were developed for determination of plasma renin activity (PRA) [31] Most of the commercially available kits for PRA determinations use modifications of the immunoassay of Haber and colleagues[30] and most investigators use similar methods Although controversy about technical details continues in the literature[3] [7] a recent cooperative study coordinated in England and embracing 17 different laboratories throughout the world appears to show that despite wide differences in units and ranges the immunoassays are accurate and reproducible and are in agreement in the ranking of high normal[31] and low values (to be published)

Physiological factors affecting renin determinations

The two most important physiologic factors affecting plasma renin activity are sodium balance and posture It is critically important that these be controlled if renin determinations are to provide clinically useful information Sodium depletion brought about by dietary restriction or by diuretic drugs sharply stimulates renin release A normogram relating plasma renin activity to 24 hour sodium excretion has been repeatedly published by Laragh and colleagues [34] The relationship of PRA to sodium balance will differ depending on the method and units used and the posture of the patient Thus laboratories must develop independent standards and cannot rely on published results of others

Both posture and physical activity stimulate renin release but of the two posture is the more important Assumption of either active or passive upright posture results in prompt rise in PRA[37] The effect of upright posture and activity are dissipated after 60 to 90 minutes in the supine position

Other physiological influences are of generally lesser clinical importance Potassium depletion stimulates renin release[3] and an important influence of the sympathetic nervous system is recognized[7] The latter is difficult to assess clinically but may be affected by medications (see below) Relatively minor influences include circadian rhythm and changes with the menstrual cycle

Influence of drugs on PRA

A majority of antihypertensive medications influence plasma renin activity either increasing or decreasing renin release Drugs which acutely stimulate renin release include all of the diuretics through their action on sodium balance and the vasodilating drugs including hydralazine diazoxide sodium nitroprusside guancydine and minoxidil Chronic stimulation of PRA is *demonstrable* in patients on long term diuretic therapy *Although classified as* renin stimulators long term therapy with certain of the vasodilators such as hydralazine results in sodium retention and suppression of renin release Inhibitors of renin release include propranolol methyldopa reserpine ganglionic blocking agents and clonidine Guanethidine appears to inhibit postural stimulation of renin release Inhibition of renin release by these drugs may be mediated through the *sympathetic nervous system* Oral contraceptives raise PRA by stimulating increased production of renin substrate

Apart from the antihypertensive group of drugs there is little information on the effects of other drugs on renin Duration of the effects of drugs following cessation of use has not been carefully studied To avoid drug influences, at least seven days should elapse between stopping medications and renin studies for most drugs and [illegible]0 days in the case of oral contraceptives

more appreciated by the physician than by the patient If the goal of surgery is 'cure' rather than 'benefit' it is evident that the methods of selecting patients for surgery at least up to the early and middle 1960s have not been excellent

Attempts to relieve renal hypertension by surgery began long before renin determinations were developed Soon after Goldblatt and colleagues[4] demonstrated that hypertension can be produced by partial constriction of the renal artery clinical reports began to appear documenting the relief of hypertension by removal of a unilaterally diseased kidney[5] Using the standard urographic methods of diagnosis available at that time many patients with hypertension and unilateral renal disease were subjected to nephrectomy This continued until enthusiasm was dampened by two critical reviews of Smith[6,7] showing that only 26 per cent of such patients were relieved of hypertension a year or more after surgery

Enthusiasm was rekindled in the mid nineteen fifties with the advent of vascular surgery and arteriography It soon became evident that angiographic demonstration of renal artery stenosis was insufficient evidence on which to base a decision to remove or revascularize a kidney for the relief of hypertension Renal artery stenosis was frequently detected in normotensive patients[8] as well Split renal function studies[10, 11] were widely used to determine whether the kidney was functionally ischemic or not In 1960 a nationwide cooperative study of renovascular hypertension was initiated in the United States Results of this study began to appear in 1972[12-19] Unfortunately the study was begun before reliable plasma renin methods were generally available and consequently no renin determination was included in the protocol There were also some variations among participants in techniques of angiography and split renal function studies

In all, 2442 patients were included in the cooperative study including 880 with various forms of renovascular disease A total of 577 operations were performed on 502 patients Considering only those patients with renal artery stenosis due to atherosclerosis or fibrous dysplasia of the renal artery, 312 patients came to surgery and results were evaluated a year or more later Adequacy of surgical repair was determined by angiography A total of 175 patients (56 per cent) were classified as 'cured,' 50 (16 per cent) as 'improved' 55 (18 per cent) as 'failed' and there were 32 (10 per cent) medical deaths Several independent series of patients have reported roughly comparable results[ ] The studies were all in general agreement that there are no distinctive clinical characteristics which set patients with remediable renovascular disease apart from patients with primary hypertension The absence of a family history onset at an unusually young or old age, the presence of an abdominal bruit and sudden acceleration of hypertension are all more common in renovascular hypertension and it is distinctly less common in blacks than Caucasians, but there is a wide overlap in all these criteria The National Cooperative Study showed that radiologic methods for detection of renovascular hypertension are valuable in case finding but of no value in selecting patients for surgery It also showed that patients with fibrous dysplasia of the renal artery generally do better following surgery than patients with atherosclerotic stenosis both in rate of cure (68 per cent vs 48 per cent) and in surgical mortality (5 per cent vs 14 per cent) Older patients and those with bilateral disease fared poorly

Renin determinations in selection of patients for renovascular hypertension

In spite of high hopes early experience with use of renin determinations for detection and selection of patients for renovascular surgery were disappointing Renin activity in peripheral venous blood was found by some to have high predictive value[ ] while others found it to have almost no value[ ] The ratio of renin activities in the two renal veins has largely replaced split renal function tests for selection of patients for surgery In general measurement of renal venous renin has been safer and somewhat more accurate for this purpose than the earlier types of tests It seems clear that in unilateral renovascular disease likelihood of surgical relief is correlated with the renal vein renin ratio A ratio of 1 5 has frequently been claimed as the critical value for surgical improvement[ ] Nevertheless the goal of accurately identifying patients likely to be cured by surgery does not seem to have been achieved up to the early 1970s[ ]

Within recent years there has been greatly enhanced understanding of a variety of variables which influence renin determinations as well as improvements in methodology of renin determi

Furthermore renin release in the opposite kidney is suppressed to or near zero Confirmation of renin dependence is shown by response to Saralasin which reduces blood pressure to normal[45, 46] This form of *two kidney* renovascular hypertension is analogous to remediable unilateral disease in man[7]

In the one kidney model renin release initially elevates blood pressure However pressure diuresis cannot occur because of the absence of the opposite normal kidney Furthermore compromise of arterial perfusion in the isolated kidney impairs sodium excretion As sodium is retained renin release is suppressed and what is initially renin dependent hypertension is converted to "sodium dependent hypertension In the first few days PRA is elevated in peripheral blood in this model and blood pressure is promptly reduced to normal with angiotensin inhibitors[1] At a later point in time sodium retention results in suppression of renin release PRA returns to normal and angiotensin inhibitors are no longer effective in reducing blood pressure

Interconversion between renin and sodium dependent hypertension has been demonstrated in the one kidney model If such animals are sodium depleted while the renal artery clip remains in place PRA rises and blood pressure becomes responsive to angiotensin inhibitors When allowed free access to sodium the depression of renin to normal (but not below) represents an intergrade with hypertension partially dependent on sodium excess and partly dependent on renin which although in the normal range may be inappropriately elevated in relation to sodium balance Because of partial sodium dependence response to Saralasin is absent or equivocal

Renovascular hypertension in man

In man renovascular hypertension spans a wider spectrum than in the experimental animal models

Patients most favorable for surgical cure of hypertension nevertheless should show most features of the renin-dependent two kidney animal model

Such patients should have (1) unilateral renal artery stenosis (2) peripheral PRA which is inappropriately high relative to sodium excretion on a constant sodium intake (3) high renal vein renin on the involved side (ratio > 1 5) (4) suppressed renin release from the opposite kidney (V A ± 0) and (5) a prompt reduction in blood pressure to normal with intravenous angiotensin inhibitor or converting enzyme inhibitor when sodium intake is restricted

Although widespread experience and prolonged follow up are still lacking experience accumulated in the past year or two suggests that patients meeting all or nearly all of these criteria have a very high likelihood of surgical cure[47]

A quick and easy method of screening patients for renovascular hypertension has long been sought Use of furosemide stimulation and PRA determinations as an outpatient screening procedure for detecting renin dependent hypertension has been proposed[4] but the accuracy of such a procedure is hard to assess Experience with both Saralasin and the nonapeptide conversion inhibitor indicates that these agents used in hospitalized moderately sodium depleted patients are remarkably reliable in identifying patients with renin dependent hypertension[5, 48] Since they do not distinguish between patients with unilateral and bilateral disease their use will not eliminate the necessity for obtaining renal vein renin determinations However data of Streeten and co workers[1] indicate that intravenous use of Saralasin in patients following four days of sodium restriction identifies with considerable accuracy those with renin dependent hypertension

Among 221 patients 32 responded with a reversible drop in blood pressure averaging 37 mm systolic and 24 mm diastolic Amost all of these patients showed elevated renal vein and/or peripheral PRA levels together with evidence of renal ischemia Of 189 patients who did not respond to Saralasin PRA was elevated in only seven (3 8 per cent) and renal vein PRA ratios were elevated in only two Response to surgery appears to be successfully predicted by Saralasin response[2] although longer follow up will be necessary for critical evaluation It seems likely that if Saralasin becomes generally available its use can simplify selection of hospitalized patients for more extensive studies In patients with negative or ambiguous responses the likelihood of surgical cure is greatly reduced Selection of patients for improvement or surgical benefit" rather than cure should be reserved for those demonstrably resistant to medical therapy and in whom an element of renin dependency can be demonstrated by use of sodium restriction angio

Importance of steady state

Stimulation of renin release by manipulation of posture, activity, sodium intake diuretics and intravenous hydralazine have been used in a variety of clinical studies to detect patients with high or low renin levels Such tests have been useful for detecting suppressed states of renin release as a screening test for primary hyperaldosteronism or low renin hypertension Acute stimulation by these maneuvers has also been used to enhance differences in renin release between the two kidneys in the selection of patients for renovascular surgery However acute stimulation combined with renal vein sampling may give misleading information, since catheterization of the renal veins is usually done sequentially, rather than simultaneously and in the presence of a rapidly rising and/or falling PRA secondary to acute stimulation differences between the two kidneys may be blunted or even reversed [1] Stimulation over a period of several days by dietary sodium restriction or oral diuretics and supine posture appears to provide steady state conditions which are more reliable for this purpose Under these conditions PRA can and should be related to 24 hour urinary sodium excretion

Competitive inhibitors for study of the renin–angiotensin system

Specific competitive inhibitors have been used in the past several years to study interrelationships of renin and sodium metabolism in experimental and clinical hypertension These are Sar[1]ala[8] angiotensin II (Saralasin) an octapeptide which specifically inhibits the peripheral action of angiotensin II[42] and SQ 20 884 a nona peptide which competitively inhibits conversion of angiotensin I to angiotensin II[43] and also influences bradykinin metabolism

Competitive inhibitors of the action of renin on its substrate have also been developed recently but have not yet been used in clinical investigation The availability of inhibitors for each step in the synthesis and activity of the renin angiotensin system provides powerful new research tools for physiological research Both Saralsin and the converting enzyme inhibitor appear to be non toxic in man Of the inhibitors available Saralasin shows the most promise for use in clinical assessment of patients It is highly specific in its action, is rapidly metabolized, and has not been shown to exert any other effect than to inhibit the peripheral action of angiotensin II

Interrelationships between renin and sodium balance in renovascular hypertension

It appears that even when posture and medications are controlled neither peripheral nor renal venous PRA is consistently reliable as an indicator of surgically remediable renovascular hypertension in patients on unrestricted sodium intake An understanding of the interdependence of sodium and renin in maintaining elevated blood pressure is essential to interpreting renin determinations in clinical hypertension Guyton and associates[44] have emphasized the importance of sodium balance in the development of sustained hypertension regardless of how it is initiated Whether acting through an effect on fluid volume, or in less obvious ways on the cardiovascular regulating mechanisms, sodium balance is of extreme importance in maintaining blood pressure under all circumstances Elevated blood pressure promotes increased renal excretion of sodium ("pressure diuresis) Loss of sodium, in turn, activates the renin-angiotensin system Finally angiotensin stimulates production and release of aldosterone, resulting in sodium retention and suppression of renin During sodium depletion, blood pressure is 'renin dependent,' and during sodium repletion it is sodium ('volume) dependent

Animal models of renovascular hypertension

An understanding of renin-sodium interrelationships in animal models is directly relevant to interpretation of renin values in human hypertension Renovascular hypertension is most reliably produced in animals by partially constricting one renal artery and removing the opposite kidney This is referred to as the one kidney model [45]

If one renal artery is constricted and the other kidney is left intact, many animals develop hypertension only temporarily, while a smaller percentage develop permanent hypertension This is the two kidney model [45]

In the two kidney model renal artery constriction activates increased renin release and blood pressure is elevated Elevated blood pressure in turn promotes increased sodium excretion ('pressure diuresis) which in many instances is sufficient to induce escape with reduction in blood pressure to normal If escape does not occur the resulting permanent hypertension can be shown to be renin dependent PRA is elevated in peripheral plasma and in the renal venous blood from the constricted kidney

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tensin inhibitors and renin determinations These will include patients with bilateral disease[47, 51] segmental disease[34] and those in whom primary hypertension has been aggravated by the development of renal artery stenosis

Value of plasma renin determinations in patients with primary hypertension

Laragh and associates[11, 15] have placed great emphasis on classification of patients with primary hypertension into high normal, and low renin groups for purposes of selecting appropriate therapy and determining prognosis It has become clear that patients with hypertension are not a physiologically homogeneous group However, more information is needed to assess the clinical value of classifying patients primarily in accordance with renin values

There is still very little data on relation of blood pressure to plasma renin activity in defined populations of normal subjects Influences of age, sex and race are known to occur but are poorly understood Lucas and colleagues[55] have shown a highly significant inverse relationship between blood pressure and plasma renin activity in normotensive subjects which is not present in hypertensives Crane and associates[56] have shown that on retesting many patients shift from low to normal plasma renin activity

Laragh and colleagues[56] have presented data in support of a hypothesis that the risk of myocardial infarction and stroke in hypertensive patients is related more to plasma renin activity than to the level of blood pressure Patients with low renin hypertension in their series were protected from cardiovascular complications[56] This hypothesis if true would imply that patients with low PRA need not be vigorously treated with antihypertensive medications and that medications which elevate PRA (eg diuretics) may actually be harmful This hypothesis has been examined by a variety of investigators and has recently been critically reviewed by Kaplan[57] The claim that cardiovascular complications are less common in patients with low PRA's has received very little confirmation or support in the data from other investigations representing large numbers of patients[7] Certainly the overwhelming bulk of available evidence supports a view that reduction of blood pressure should be pursued vigorously in hypertensive patients regardless of whether PRA is high normal, or low

Plasma renin in relation to selection of antihypertensive medications

It has become apparent that patients with primary hypertension differ in the extent to which abnormalities in peripheral resistance, cardiac output, plasma volume the renin-angiotensin-aldosterone system and the sympathetic nervous system contribute to elevated arterial pressure Antihypertensive medications differing in mechanism of action can theoretically be fitted to the abnormalities of individual patients[3] Patients with high PRA levels have been shown to respond well to propranolol used alone[57] while patients with low PRA and high plasma volume respond to vigorous diuretic therapy[3] The desired goal of preselecting appropriate drugs on the basis of physiologic characteristics in individual patients is still largely hypothetical[34]

Physiologic variables may vary over time in the same individual[34] Patients often vary unpredictably in hypotensive responsiveness and ability to tolerate drugs Prospective clinical studies are needed to determine the accuracy of prospective individualized therapy Meanwhile an element of empiricism is appropriate, and patients should not be denied any antihypertensive agent on the basis of PRA or other physiological measurements

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Annotations

Coronary care units

Considering the vast amount of medical literature appearing every year it is rather surprising that some major medical problems are unsettled for a considerable length of time or remain completely unsolved. Examples are the value of cytological screening for uterine cancer the prophylactic benefit of regular physical check ups, the importance of anticoagulation therapy in coronary thrombosis and the effectiveness of coronary care units in lowering mortality rate from myocardial infarction All are problems of the greatest interest to society and the medical profession

When coronary care units (CCU) were introduced a decade ago it was thought that the achievements of the electronics industry would make it possible to detect cardiac arrhythmias early and by prompt treatment favorably influence the hospital mortality rate In addition the study of the course and complications of acute myocardial infarction and the effect of different drugs on these would be greatly facilitated

It is noteworthy that the number of CCUs grew far more rapidly than experience could be gained In a recent paper by Bloom and Peterson, it is shown that CCUs in Massachusetts are far too numerous. Without any inconvenience to the patients a reduction in the number of CCUs (from 94 to 39) would lead to substantial savings probably together with increased effectiveness.

Most interesting is that even by now no definite proof as to the benefit on the mortality rate from acute myocardial infarction has been established. Although a number of papers to this effect have been published no well-controlled study has as yet been reported On the contrary some papers—although not statistically infallible—have been presented pointing to the fact that although extensive resources have been spent on CCU no reduction of the mortality rate has been obtained. It is of interest that some papers reporting a considerable lowering of the mortality rate from acute myocardial infarction do not meet even modest demands as to the statistical analysis of the results obtained—for example by giving no control figures

In a forthcoming paper by the present authors it is shown that 20 per cent of the patients admitted with infarction did not have the correct diagnosis suspected soon enough to be treated [illegible] the CCU The mortality rate [illegible] such patients was much higher than in the rest and would bias mortality rate figures from hospitals or departments without CCU compared to those with CCU It [illegible] also demonstrated than even very small differences in the diagnostic criteria can lead to considerable discrepancies in the total mortality rate when hospitals or departments are compared

One of the theoretically valuable points of CCU is that cardiac arrhythmias could be detected and treated immediately It is however surprising that the papers [illegible] reporting the results of controlled studies on the effectiveness of the most widely used antiarrhythmic drug—lignocaine—concluded that no effect of prophylactic treatment could be detected with lignocaine on the mortality rate from myocardial infarction. It would have been fair to assume that by now the value of lignocaine would have been definitely assessed and the consequences taken.

Nobody with any experience from a CCU will deny that these units do offer a certain marginal gain as some patients are resuscitated who would otherwise have died Probably this would be true for many other diseases provided the patients were (or could be) as carefully supervised as in a CCU However with the rising (and now often stupendous) cost for medical care it must be claimed that the uncertainty concerning the benefit of CCU be solved, although this might turn out to be a difficult decision to make Several well controlled trials should be set up taking the cost the drain on medical manpower and the influence on mortality rate into account. The mortality rate should be judged not solely from the total number of lives saved but also on the total years of life the CCU would be supposed to have saved

The results might reveal the cold fact that even when large resources are used the outcome might be poor and that the funds spent in lowering the mortality rate from myocardial infarction a few per cent might have been applied elsewhere with much more benefit.

However by now at least one point could probably be agreed upon It would have been less costly and far more informative to have set up initially a limited number of well staffed and well-equipped CCUs to study the effectiveness and value of these units before investing on a large scale in CCUs around the world.

J Lindholm M.D
N Fabricius Bjerre M.D
K Asvad M.D
J Kjærulff M.D
Bispebjerg University Hospital
Medical Department
Copenhagen NV 2400
Denmark

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Chemical incompatibility of Renografin 76 and protamine sulfate

The chemical incompatability of various drugs and contrast media preparations is well recognized Marshall and colleagues investigated reactions occurring between contrast media and antihistamines More recently Holman and Dewanjee demonstrated the effect of pH on precipitation of organic iodides by a variety of pharmaceuticals

The problem of chemical incompatabilities has special pertinence to coronary arteriography Prior to 19 0 a high incidence of thromboembolic phenomena were noted by several workers Subsequently Eyer[3] noted a marked decrease in embolic complications when catheterization procedures included the injection of 5 000 units of heparin following arterial puncture and 50 mg of protamine sulfate at the conclusion of the procedure Hawkins and Herbert demonstrated that contrast media used as flushing agents were more effective in preventing thrombosis than was heparinized saline

At the present time systemic heparinization is utilized during coronary arteriography performed by the percutaneous transfemoral technique in many cardiac catheterization laboratories. Many arteriographers also neutralize the heparin with protamine sulfate at the end of the procedure On occasion the protamine sulfate is administered directly into the arteriography catheter When this was done in our laboratory with the catheter filled with meglumine diatrizoate and sodium diatrizoate injection (Renografin 76) a precipitate was observed to form in the syringe To investigate this phenomenon a series of experiments was performed

A No 5 standard polyurethane preformed coronary catheter was loaded with Renografin 6 Forty mg of protamine sulfate solution was then injected through the catheter This resulted in a thick whitish gel which was expressed at the distal end of the catheter This precipitate did not dissolve after standing 24 hours at room temperature or after heating the precipitate to body temperature A hard crystalline button formed when the precipitate was allowed to settle (Fig 1) Slow dissolution followed tenfold dilution with water but insoluble material was still present at three hours Precipitate also formed when protamine sulfate was added to a 1 1 volume mixture of Renografin 6 and serum at 37 C A

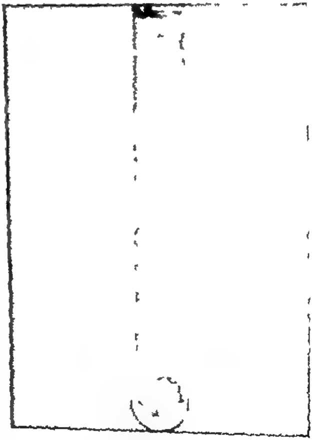

Fig 1 Precipitate observed following addition of protamine sulfate to Renografin 76

catheter filled with Renografin 76 was then flushed with 50 c.c of saline Forty mg. of protamine sulfate solution was then injected through the catheter A visibly detectable and soluble material resulted however this material was much less dense than when the catheter had not been flushed Since the pre

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Norepinephrine—The myocardial hypertrophy hormone?

What causes myocardial hypertrophy? Experimentally hypertrophy has been produced by several methods as re viewed by Fanburg these methods fundamentally consist of (1) an increase in preload e g systemic AV fistulas and (2) an increase in afterload e g obstruction or banding of the pulmonary artery or aorta and systemic hypertension Physi cal exercise has also been utilized for stimulation of myocar dial hypertrophy in animals this latter method is a more complex stimulation of myocardial hypertrophy and is prob ably a combination of the above two mechanisms All of these methods result in an increase in ventricular wall tension which has been suggested as being the trigger for the hyper trophy process However how is a physical stimulus such as wall tension translated to the biochemical level to result in increased protein synthesis and myocardial hypertrophy? Evidence has accumulated that norepinephrine may play an important role in the hypertrophy process In 1970 Gans and Cater reported that norepinephrine produced cardiac hyper trophy in dogs however these investigators used hypertensive doses of norepinephrine leaving unanswered the question of whether the norepinephrine induced myocardial hypertrophy is simply the effect of the increased afterload of hypertension or a direct effect of norepinephrine on the myocardium We eliminated hypertension as a potential factor by utilizing a subhypertensive dose of norepinephrine in conscious dogs Blood pressures were closely monitored to ascertain that they remained at normal levels After periods of 8 to 63 weeks a significant degree of left ventricular hypertrophy was pro duced in spite of the fact that blood pressure had remained in the normotensive range Thus this was the first clear evidence that norepinephrine in subhypertensive doses could directly induce ventricular hypertrophy That norepinephrine may in fact be an important intermediate in the physiologic hyper trophy process is further suggested by a study of Ostman and colleagues in which cardiac norepinephrine concentrations were measured in exercised rats After 15 weeks of exercise a 7 per cent increase in heart weight was found in the exercised rats as compared to controls Significantly a 16 per cent increase in cardiac norepinephrine concentration was demon strated in the rats with mild cardiac hypertrophy

Consequently the hormone norepinephrine appears to be important for the induction of myocardial cellular growth We consider the following mechanism to be important in the production of myocardial hypertrophy an increase in after load or preload results in an increase in ventricular wall tension which in turn stimulates release of norepinephrine by the sympathetic nervous system into the myocardium Nore pinephrine then brings into action the biochemical machinery necessary for the hypertrophy process Of note norepine phrine may also be released by other methods e g neural reflexes Chronic excessive stimulation of the release of nore pinephrine may lead to exhaustion of this system and deple tion of norepinephrine in the myocardium thereby limiting the hypertrophy process as occurs in the chronically over loaded heart the eventual outcome of the process is decom pensation Several studies have demonstrated a decrease in myocardial norepinephrine content both in experimentally induced congestive heart failure and in patients with natu rally occurring congestive heart failure Thus with chronic stress to the heart a decrease in norepinephrine may be the factor that limits the degree of compensatory hypertrophy eventually resulting in chronic heart failure

In summary we consider that the existing evidence impli cates norepinephrine as playing an important role in the hypertrophy process Norepinephrine may be the hormone that initiates myocardial hypertrophy in response to an increase in ventricular wall tension

Michael M Laks M D
Fred Morady B A
Harbor General Hospital
1000 W Carson St
Torrance Calif 90509

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Of questions

How many Americans are hurt on the treadmill annually? How many die annually because of the treadmill? Who is or are legally accountable the manufacturers who push the equipment in their sales programs or the doctors who use the treadmill in their practice? Do more Americans die because of Dye No 2 or because of the treadmill?

G E Burch M.D
Tulane University School of Medicine
and Charity Hospital
New Orleans La

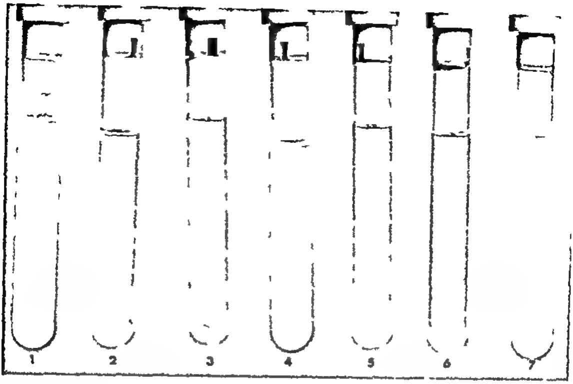

Fig 2 Dilution experiments Tube No 1 (1 1 admixture of Renografin 76 and protamine sulfate) through tube No 7 (addition of protamine sulfate to a 20 per cent volume/volume solution of Renografin 76) See text for detailed description

cipitate dissolved following dilution with water and as both solutions were near saturation additional experiments were performed to determine if the precipitate resulted from an incompatability or insolubility phenomenon

The dilution experiments are demonstrated in Fig 2 The tube on the far left tube No 1 is a 1 1 admixture of Renografin 76 and protamine sulfate A thick gelatinous precipitate is visible The second tube contains a 1 10 dilution of this 1 1 admixture and demonstrates dissolution of the precipitate In the third tube a 1 per cent volume/volume solution of Renografin was prepared To 50 ml of this solution 5 ml of protamine sulfate solution was added dropwise without evidence of insolubility In the fourth tube the order of addition was reversed by adding Renografin 76 to a tenfold dilution of protamine sulfate Immediate clouding appeared followed by clearing up to a total added volume of 3 5 ml of Renografin 76 Additional volume beyond this amount resulted in a persistent visible haze in the admixed solution In the fifth tube 20 ml of Renografin 76 was added to 500 ml of normal saline giving a 4 per cent volume/volume solution Twenty ml of protamine sulfate was then added No clouding or precipitation occurred at the time of addition and the solution remained clear after three hours In the sixth tube a 10 per cent volume/volume solution remained clear after addition of protamine sulfate In the seventh tube addition of protamine sulfate to a 20 per cent volume/volume solution of Renografin 76 resulted in a definite visible haze

The possibility that acid pH caused the precipitate was investigated The pH values for Renografin 76 and protamine sulfate are in the ranges of 7 0 to 7 ■ and 6 0 to 7 0 respectively A 1 1 volume admixture of Renografin 76 and protamine sulfate at 37 C resulted in a pH of 6 7 well above the acid range noted to cause precipitation of organic iodides[1]

In summary the admixture of protamine sulfate to Renografin 76 resulted in a gel precipitate which dissolved slowly when diluted tenfold with water Protamine sulfate did not cause precipitation when added slowly to a 1 per cent volume/volume solution Addition of Renografin 76 to diluted protamine sulfate did cause clouding and haze These results confirm the potential for precipitation in mixtures of protamine sulfate and Renografin 76 especially when Renografin 76 is added to a solution containing protamine sulfate These data do not make clear whether precipitation results from a compatability or solubility problem Precipitation does not appear to be on the basis of low pH The appearance of a precipitate when the concentration of Renografin 76 is increased and the loss of precipitate with dilution suggest a solubility problem Although no adverse clinical events have been observed due to this precipitation phenomenon it is recommended that if protamine sulfate is used to neutralize heparin it should not be administered through the arteriography catheter

Carroll M Martin M D F A C C
Grant Taylor M D
Cardiology Service and
Department of Medicine
Madigan General Hospital
Tacoma Wash 98431

The authors wish to express their thanks and appreciation to Doctor G C Chiu of the Clinical Investigation Division of the Lilly Research Laboratories for his advice in the preparation of the dilution experiments

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Table I Typical results obtained from one patient undergoing cardiac catheterization

Sampling site	*Hemoglobin (gm %)*	*Oxygen saturation (%)*	*Measured oxygen content† (vol %)*	*Derived oxygen content (vol %)*
IVC	12.3	5.5	12.4	12.9
High SVC	11.3	67.3	10.8	11.5
Mid SVC	11.8	0.4	11.5	12.1
Low SVC	12.3	70.3	11.8	12.1
High RA	12.1	87.0	13.8	14.9
Low RA	12.3	88.3	14.5	15.1
High RV	14.3	88.7	17.0	15.1
Mid RV	12.9	89.6	15.8	15.3
Low RV	13.1	87.3	15.8	15.0
Low PA	12.6	89.2	15.3	15.2
High PA	13.7	87.1	16.5	14.9
LV	11.9	87.8	14.3	15.0
LV	12.6	87.4	14.5	15.0
LV	12.6	88.7	15.2	15.1

Hemoglobins were measured using a Coulter Counter Model S
†Oxygen contents were derived from the formula

$$\frac{1.34 \times \text{mean Hb (gm \%)} \times O_2 \text{ sat. (\%)}}{100}$$

markedly (Table I) Presumably this may be attributed to sample errors introduced by use of the cardiac catheter Since oxygen content is proportional to both hemoglobin concentration and oxygen saturation indiscriminate changes in hematocrit will tend to invalidate quantitative comparisons between blood samples from different sites.

Although we still believe direct estimations of blood oxygen content to be superior to those derived from saturation values, we are now convinced that during cardiac catheterization saturation measurements are more meaningful because they are not dependent upon the hematocrit If an average value of hemoglobin concentration is chosen from which the content for each measurement of oxygen saturation can be calculated the effect of sampling errors will be minimized

Lewis Adams B.Sc.
Peter Cole F.F.A R C.S
Anaesthetics Laboratory
Department of Anaesthesia
St Bartholomew's Hospital
London EC1A 7BE
England

REFERENCE

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Letters to the Editor

Energy levels of commercial defibrillators revisited

To the Editor

We read with considerable interest the letter from Dr P F Fazzini (AM HEART J 90 409 1975) in which it is stated that in the reference cited (Ref 1 his letter) we recommend that *defibrillator output be increased* The reference cited relates to defibrillation with electrodes directly on the heart and the statement Dr Fazzini made regarding the ability of present day defibrillators to defibrillate subjects weighing 50 kg and over came from a paper that he did not reference In fact we have reported that direct defibrillation requires energy levels lower than generally used In addition Dr Fazzini claims that there is doubt whether we reported indicated or delivered energy We *always* report delivered energy For example in our Ref 1 below it is stated The percentage of indicated energy actually delivered was measured Energy values recorded in the patients charts were then converted to delivered energy

We and our co authors hope that this explanation will clarify Dr Fazzini s problem We also request that this letter be published as a response to Dr Fazzini s criticism

L A Geddes M E Ph D
Director Biomedical Engineering Center
W A Tacker Jr M D Ph D
Electrical Engineering Building Room 32
Purdue University
West Lafayette Ind 47907

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Reply

To the Editor

We sincerely thank Drs Geddes and Tacker for their kind and clarifying answer

It was our interest to stress the concept that discussions and comparisons between defibrillators can be made only by converting the indicated energy into delivered energy and we are glad to see that Drs Geddes and Tacker have the same opinion

Nevertheless it still remains uncertain if in man failure or success of ventricular defibrillation can be evaluated considering only *two parameters—level of delivered energy* and body weight of the patient Perhaps also the circumstances underlying the arrhythmia have some importance In our experience a successful result (conversion of ventricular fibrillation to another cardiac rhythm without regard to ultimate survival) was obtained in 97 per cent of cases of primary ventricular fibrillation (arrhythmia occurring in the absence of shock or advanced heart failure) while the same result was attained in only 70 per cent of cases of secondary ventricular fibrillation (arrhythmia occurring in patients with circulatory failure)

PierFilippo Fa ini
Francesco Marchi
Saverio Torrini
Department of Cardiology
Arcispedale S Maria Nuova
Firenze Italy

A commentary on hypertension

To the Editor

AUSCULTATION

After due consideration
I have found that auscultation
Demands great concentration
(And some imagination)
Since there is no calibration
For that instrument we call the human ear

But physicians don t lo e heart
Remember medicine s an art
And its most important product is good cheer!
So just tell the nice old lady
It s one twenty over eighty
And don t worry over what you think you hear

Alvin H Sacks Ph D
Bioengineering and Physiology Division
Palo Alto Medical Research Foundation
860 Bryant St
Palo Alto Calif 94301

Measurement of blood oxygen content

To the Editor

The measurement of blood oxygen content by direct means (i e extraction with subsequent estimation) has been considerably simplified by the recent development of a new technique (the Lex O_2 Con) We have suggested that this method might be used to advantage in the determination of blood oxygen contents during cardiac catheterization However more recent experience has shown that results obtained during such routine procedures can often be confusing Closer examination of the problem has revealed that hemoglobin concentrations (and hematocrits) of serial samples taken from a single patient during catheterization can vary quite

Books received

How to Live with Your Heart By Arthur Vineberg M D New York, 1975 Quadrangle 213 pp Price $8 95

Circulation Research Vol 36 No 6 June 1975 Hypertension Research 1974 Clinical & Experimental Edited by Norman M Kaplan New York 1975 American Heart Association 269 pp Price $6 00

Surgical Treatment of Congenital Heart Disease By Grady L. Hallman M D and Denton A Cooley M D Philadelphia 1975 Lea & Febiger 204 pp Price $18 50

Genetic Screening Programs Principles and Research National Academy of Sciences Committee for the Study of Inborn Errors of Metabolism Washington D C., 1975 National Academy of Sciences 378 pp Price $6.00

Book reviews

Performance Ventriculaire Gauche chez l Homme Edited by P Besse and H Bricaud Paris 1975 Expansion Scientifique Francai■ 496 pages

This publication contains the presentations at a symposium on the performance of the left ventricle of man held in Bordeaux during September 9 10 1973 The mechanical aspect of the cardiac pump is well discussed The use of concepts in bioengineering computer analysis mathematics and physical principles are nicely discussed As would be expected cardiac angiography provided a great deal of data for the discussions The performance of the left ventricle in various types of heart disease such as ischemic heart disease i extensively presented This is a good review of the studies and theoretic discussions of left ventricular function The book should interest all cardiologists bioengineers biophysicists and physiologists

Epidemiology and Control of Hypertension Edited by Oglesby Paul M D New York 1975 Stratton Intercontinental Medical Book Corporation 691 pages Price $24 75

Paul has edited a book which should interest epidemiologists more than practicing physicians The incidence of hypertension in man is fairly well known Hypertension is certainly well known to be an extremely important daily problem in the practice of medicine These proceedings of an international symposium provide interesting aspects of the incidence of hypertension among twins spouses migrants and nationals Dietary pediatric therapeutic and preventive aspects of hypertension are discussed Such symposia remind everyone of the importance of the subjects discussed The proceedings also provide information for those with special interests This is a good reliable publication

Recent Advances in Studies on Cardiac Structure and Metabolism vol 6 Pathophysiology and Morphology of Myocardial Cell Alterations Edited by A Fleckenstein and G Rona Series editor G Rona Baltimore/London/Tokyo 1975 University Park Press 551 pages Price $39 50

This sixth volume on cardiac structure and metabolism like the five preceding ones ■ an excellent publication Investigators interested in muscle anatomy physiology and metabolism should find this volume not only interesting and important but worth owning for study and reference The contributors are outstanding investigators and their studies are important This volume for example consists of several papers concerned with such problems as myocardial fiber necrotization from intracellular calcium overload isoproterenol induced disorders of myocardial metabolism role of calcium in hereditary cardiomyopathy of the Syrian hamster ultrastructural manifestations of hypoxia and ischemia noncoronarogenic myocardial cell injury myocardial cell damage produced by viruses and others The publication is of high quality physically, e g the paper is excellent the illustrations clear the author and subject indices are good and the format is well organized This ■ a very important book that summarizes the symposium held in Freiburg in September 1973

Care of the Cardiac Surgical Patient By Ouida M King R N., Saint Louis 1975 The C V Mosby Company 276 pages Price $12.95

This small textbook type publication on the surgical care of the patient with heart disease is different in that it is directed at the care of the surgical patient by nurses technicians and physicians The fundamental aspects of cardiac disease anatomy physiology pathology and surgical technic are succinctly discussed The use of modern diagnostic procedures operative procedures including the artificial cardiopulmonary bypass pump hypothermic and other prostheses are discussed Preoperative and postoperative care of the patient is discussed and well supported by well selected illustrations The cardiovascular intensive care unit is well presented Cardiologists surgeons nurses and technicians and trainees will find this to be a useful book worth studying and owning as a reference

Primary Pulmonary Hypertension Report on a WHO Meeting Edited by S Hatano and T Strasser Geneva 1975 World Health Organization 45 pages

This 45 page pamphlet reports the transactions of a WHO meeting held in Geneva during October 1973 on primary pulmonary hypertension The disease ■ classified described its clinical features and etiology briefly discussed and management recommended The disease is rare but it is serious highly fatal and its cause unknown All physicians in the non surgical specialties will find this pamphlet worth owning

The Cardiac Conducting System and the His Bundle Electrogram By Nigel Keith Roberts M D New York 1975 Appleton Century Crofts 179 pages Price $12 95

This small book briefly reviews very well the history anatomy function disturbances in function and management of diseases of the conduction system Roberts reviews the history and anatomic studies of the conduction system The His bundle electrogram ■ clearly discussed The role of the Bundle of His in clinical disturbances in cardiac rhythm is presented with well selected illustrations and legends Clinical states related to disturbances in function of the conduction system and their management are presented for the practicing cardiologist Even though Roberts is a pediatric cardiologist trainees in adult cardiology also will find this to be a useful book to study and own

American Heart Journal

June 1976 Volume 91 Number 6

Editorial

Coronary thrombosis: Facts and beliefs

Giorgio Baroldi, M.D.
Pisa and Milan, Italy

The idea that coronary thrombosis is a secondary event following infarction is provocative and deserves serious consideration. Presently a substantial body of knowledge supports the classic concept of the primary role of thrombosis in pathogenesis of infarction. This is the conclusion of a workshop on the role of the coronary thrombosis.[1] The main points of such a body of knowledge can be summarized as follows: (1) presence of an occlusive thrombus in most of the large transmural infarcts; (2) its location in arterial vessels supplying the infarcted area (spatial relation); (3) correlation between its age and that of the infarct (chronological relation); (4) rupture or ulceration of an atherosclerotic plaque as primary cause of the thrombus formation; (5) lack of documentation that collaterals may compensate within 30 minutes (estimated time for ischemic necrosis to occur) a severe blood flow reduction in the extramural coronary arteries. On that basis the low frequency of coronary thrombosis reported in the literature has been interpreted as due to erroneous methods of examination or incorrect definition, the examined material being a miscellany of unrelated patterns (small infarcts, large infarcts, sudden death cases).

The last criticism, however, cannot be applied to those studies in which the subjects died in the course of treatment for a classical clinical pattern of acute cardiac infarct without other cardiac disease, not having undergone any surgical procedure, and with histologic documentation of a typical coagulation necrosis. Cases of recent fibrosis without residual foci of the latter have to be discarded. The fibrous tissue, in fact, is an anomalous nonpathognomonic end result of any irreversible myocardial damage.

One hundred selected cases constitute the basis for the present discussion, which will first consider the distinction between small and large infarcts. In general, small infarcts may be defined as multifocal patchy necroses, often subendocardial, not or rarely associated with an occlusive thrombus, secondary to a relative acute coronary insufficiency or to a variety of proposed pathogenetic mechanisms. In contrast, true infarcts are large unifocal transmural lesions due to an occlusive thrombus. The first question, therefore, is to determine the critical size between the two entities. Some speak of 2.5 cm in length and width, since in 91 per cent of infarcts of such or higher dimension there was an occlusive thrombus. Others reported a 96.5 per cent frequency in infarcts with a diameter greater than 4 cm, and below it the incidence of occlusive thrombus fell to 55 per cent. These two examples emphasize the difficulty in outlining the critical size. Due to the irregular tridimensional shape of the coagulation necrosis, estimation of its dimension by measuring its diameters may be inaccurate. Furthermore, a 2.5 cm infarct is a relatively small infarct when found in a highly hypertrophied heart. In our study the size of the infarct was calculated as volume percentage of the coagulation necrosis with respect to the total left ventricular mass, including the whole interven

From the C.N.R. Clinical Physiology Laboratory [illegible] the University of Pisa [illegible] Pathology, Medical School, University of [illegible]

Received for publication [illegible] July [illegible] 1975

Reprint requests: Dr. Giorgio Baroldi, C.N.R. Laboratory of Clinical Physiology, [illegible] Via P. S[illegible] 8, 56100 Pisa, Italy

Announcements

Congress on thrombosis and hemostasis

The sixth congress of the International Society on Thrombosis and Haemostasis will be held in Philadelphia from June 26 through July 2 1977 at the Marriott Hotel City Line Ave Bala Cynwyd Pa Deadline for abstracts is February 15 1977

All requests for information regarding this congress and all correspondence should be addressed to VIth Congress Thrombosis and Haemostasis Thrombosis Research Center 3400 N Broad St Philadelphia Pa 19140

Third International Congress on Electrocardiology

The third International Congress on Electrocardiology will be held in Brussels Belgium on June 28 29 and 30 1976 The main theme of this year s Congress will be The ECG What is it good for in the early detection of coronary heart disease and for its prognosis? The official language of the Congress is English

For additional information concerning papers films and exhibitions for the Congress and for registration forms please write 3rd International Congress on Electrocardiology Vrije Universiteit Brussel School of Medicine Unit for Cardiovascular Research Eversstraat 2 B 1000 Brussels Belgium

Cardiovascular stress testing seminar

A nation wide Cardiovascular Stress Testing Seminar will be held June 10 through 13 1976 at the Convention Center Little Rock Ark The seminar is sponsored by the Division of Cardiology University of Arkansas for Medical Sciences and by the Council of Clinical Cardiology This Continuing Medical Education offering meets the criteria for 17 hours of credit in Category I for the Physician s Recognition Award of the American Medical Association and 17 hours of Prescribed AAFP credit have been requested Early preregistration is required since enrollment is limited

For further information please contact John Douglas M D University of Arkansas for Medical Sciences 4301 West Markham Little Rock Ark 72201 Telephone (501) 664 5000 ext 188

Association of Army Cardiology meeting

The fifth meeting of the Association of Army Cardiology titled Advances in Cardiovascular Disease will be held at Fitzsimons Army Medical Center on May 13 through 15 1976 For further information please write William P Nelson M D Colonel MC Chief Cardiology Service Box 6295 Fitzsimons Army Medical Center Denver Colo 80240

American Heart Journal

June 1976 Volume 91 Number 6

Editorial

Coronary thrombosis: Facts and beliefs

Giorgio Baroldi, M.D.
Pisa and Milan, Italy

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From the C.N.R. Clinical Physiology Laboratory at the University of Pisa and ... Medical School, University of Milan ...

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Reprint requests: Dr. G. ... Baroldi, C.N.R. Laboratorio di Fisiologia Clinica, Università di Pisa, Via P. Savi 8, 56100 Pisa, Italy.

Table I Infarct size vs survival time and frequency of occlusive thrombosis

Infarct size (%)	*Survival time (days)*						*Total cases*			
	< 2		*3 10*		*11 25*		*Total*		*Occl thr*	
	Total	*Occl thr*	*Total*	*Occl thr*	*Total*	*Occl thr*	*No*	*%*	*No*	*%*
< 10	19	2	6	—	4	2	29	100	4	13 7
11 20	6	—	5	2	9	5	20		7	35 0
21 30	4	1	16	8	5	1	25		10	40 0
31-40	[illegible]	2	4	2	4	1	11		5	45 4
41 50	—	—	5	5	7	4	12		9	75 0
51 60	—	—	2	2	1	1	3		3	100
Total	32	5	38	19	30	14	100		38	
Per cent	100	15 6	100	50	100	46 6				

Table II Lack of correlation between infarct size and number of main coronary arterial vessels with severe stenosis

Infarct size (%)	*> 70% stenosis in*						*< 70% stenosis to normal*		*Total*	
	1 (%)		*2 (%)*		*3 (%)*					
	No	*%*	*No*	*%*	*No*	*%*	*No*	*%*	*No*	*%*
< 20	16	32 6	19	38 7	9	18 3	5	10 0	49	100
> 20	23	45 0	17	33 3	5	9 8	6	11 7	51	100
Total	39		36		14		11		100	

tricular septum From Table I it can be seen that the size of the infarct ranged from less than 10 to 60 per cent of the total left ventricle the incidence of an occlusive thrombus from 13 7 to 100 per cent, with an increase directly related to the increase of the infarct size the over all frequency being 38 per cent *Only 15 cases showed a multifocal patchy* coagulative necrosis (12 of which were subendocardial i e located in the internal one fourth of the wall) all involving less than 10 per cent of the left ventricle and not associated to an occlusive thrombus On the other hand in most of the 15 cases with a size greater than 41 per cent, the latter was present Therefore out of 100 clinically and morphologically documented infarcts, only 30 can be defined according to the classic view The main question is how to define the other 70 cases with (1) 'unifocal and regional coagulation necrosis, (2) a diameter in general much larger than 2 5 to 4 cm , (3) an extension involving one half or more of the septal or free ventricular wall i e , transmural according to the ambiguous definition adopted by the workshop' (4) a relatively low frequency of occlusive thrombi (less than 50 per cent Table I) Are these small infarcts or what?

In reality it is practically impossible to quantify a critical size and therefore to distinguish between small and large infarcts on the basis of the presence (or absence) of a thrombus The facts are that even large transmural infarcts are frequently unrelated to an occlusive thrombus and that the clinical course and mortality rate are not related to the size of the infarct (Table I) the only peculiar finding being a shorter survival time in smaller infarcts A secondary transmural progression of a primary subendocardial or *internal coagulation necrosis was not observed* The frequent extension of the myocardial damage was due to other types of myocardial necrosis[7]

On that basis, without any clear cut clinical and morphological distinction the classic definition becomes questionable if not unsustainable, and of little—if any—value in supporting the idea

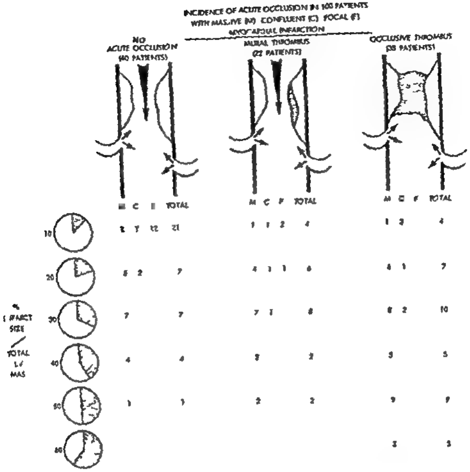

Fig 1 *Incidence of acute occlusion in 100 patients with massive confluent or focal myocardial infarction M = massive myocardial infarction C = confluent myocardial infarction F = focal myocardial infarction*

of the primary role of the thrombus The impression is that the sustainers of the classic concept seem to preconceivedly define an infarct as large when a thrombus is present disregarding many other basic variants In fact the frequency of the occlusive thrombus as well as of the nonstenosing mural one correlates not only with the size but also with the massive type of the coagulation necrosis (Fig 1) the degree of the pre existing very old stenosis its length (Fig 2) and the prevalence of atheromatous material in the latter

No correlation was found with survival time (the lower figure in the 2 day survivors (Table I) being likely due to the prevalence of small sized infarct in this group) size of myocardial scar heart weight, hypertension anticoagulant therapy and or terminal irreversible shock

Before considering the possible significance of the previous relationship let me first discuss the other items of this substantial body of knowledge The other two points in favor of the primary role of the thrombus namely its spatial and chronological relation are inconsistent In fact both can be expected even in the case of a secondary thrombus If the infarct is the cause the thrombus will occur in the supplying vessel at the same approximate time taking for granted our limited capacity in timing vascular and myocardial lesions in man

Another debatable assumption is that the primary erosion or ulceration of the atheromatous plaque is a frequent event linked with the genesis of the thrombus If true the easily recognizable embolization of atheromatous material should be an equally frequent event in the intramural vessel in any pattern of coronary disease In our experience this is not the case and in the extremely rare instances one cannot exclude the aortic origin of the embolus This negative finding

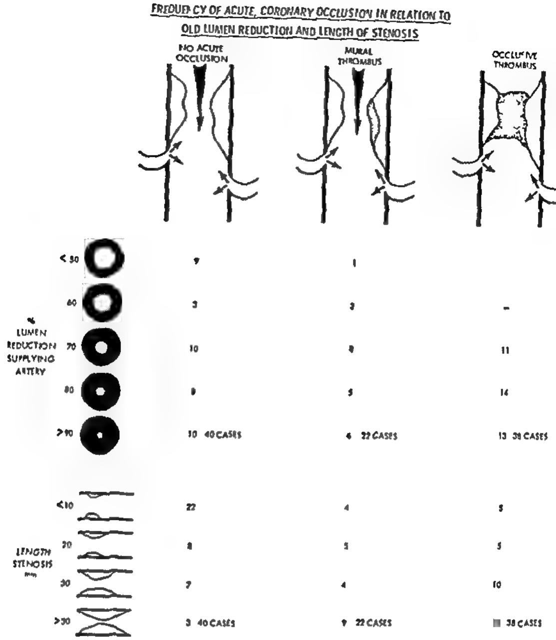

Fig 2 Frequency of acute coronary occlusion in relation to old lumen reduction and length of stenosis

suggests that the erosion can be either an artifact or due to the damaging effect of the thrombus itself or to the secondary changes at the site of the stenosis following an infarct.[8] The latter appear to be of paramount importance in the present discussion particularly in relation to the belief that the collaterals are not functioning. The compensatory capability of an acute occlusion by the extremely numerous normal collaterals[7] is still an open question.[9-11] On this subject we must bear in mind that in most instances the infarct size is only a part—and often a small part (Table I)—of the vascularization area of the occluded vessel. Furthermore, the surgical ligature of the bleeding anterior descending branch due to chest injury in two young healthy men was not followed by an infarct.[1,11] Only two but nevertheless significant cases. However, in the natural history of coronary heart disease three facts must be kept in mind: (1) The occlusive thrombus is never found in a normal coronary artery; on the contrary, it is always located in a vessel with an old severe stenosis. (2) All the cases of acute infarct associated with severe, old obstructive coronary damage show a significant increase in diameter and length of the normal collaterals proportional to the degree and extension of the old vascular injury. (3) The identical increase is visible in the cases with the same degree of coronary damage but without infarct

(about 50 per cent of the total population who die in hospital with severe coronary arterio athero sclerosis)[6,7] This means that the enlarged collaterals seem to adequately compensate the obstructive lesions in many subjects without evidence of coronary disease as well as in coronary patients for long time before the onset of the disease No proof exists that the latter is due to a sudden insufficiency of these vessels which can be demonstrated—even if partially —in vivo by cineangiogram Furthermore if the morphologically proved anastomoses were incompetent one would expect that the size of the infarct correlates with the number of the severely stenosed vessels The contrary is shown in Table II Finally the occlusion of an experimental stenosis (25 per cent of the control flow) maintained for a few days did not result in an infarct ventricular fibrillation or impairment of the cardiac dynamics By cineangiogram and post mortem injection a dramatic increase of the collaterals was demonstrated[9] This experiment mimics what happens in coronary heart disease confirming the capability of the collaterals to become competent in a relatively short time and the little if any ischemic significance of the thrombus because of the already protecting collaterals Their active presence also suggested that a thrombus could be a secondary phenomenon A concept supported by its relationship with the previously reported variants In fact the thrombus links with (1) severe and long stenosis i e increase retrograde collateral flow antagonizing the reduced proximal flow (2) atheromatous stenosis i e loss of fibrinolytic activity of the atheromatous vessel wall (3) massive and larger infarct i.e increased peripheral resistance (blockage of the intramural flow proportional to the dimension and massiveness of the coagulation necrosis with lost of contractility paradoxical bulging stretching of the cardiac wall and subsequent interstitial edema exudation and vascular thrombosis) and secondary stenosis in the supplying vessel[4] and hindrance of blood flow in the residual lumen and in the recanalizing channels at the level of the stenosis

The claim that the thrombus if secondary should be connected with the infarcted area—in other words, it should fill the whole supplying vessel—does not consider that the target area for all these interrelated thrombogenic factors is the stenosis the stasis in the generally normal distal tract resulting in a redistribution of the flow by the collaterals to the normal myocardium surrounding the infarct

In conclusion the discrepancy in the incidence of coronary thrombus can be explained by the selection of the material It sounds likely that if only cases with extremely severe long 'atheromatous stenosis associated with a 50 per cent infarct size are selected the thrombus frequency can be 100 per cent which does not prove that the thrombus is the cause of the infarct

At present despite some controversial attempts[1] the secondary thrombus formation has not yet been demonstrated In a 'human experiment however a stenosis bypassed by a vein graft may occlude in relatively short time [19] In this condition the bypass flow may be assimilated to a very high collateral flow—a fact which further supports the hypothesis of a secondary thrombus formation as well as the secondary progression of an arterio atherosclerotic plaque by mural thrombi

In conclusion one is tempted to paraphrase the workshop statement by saying that the classic concept of the primary role of the thrombus still deserves serious consideration Presently however a substantial body of knowledge supports the concept of a secondary genesis of the thrombus

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Clinical communications

Atrial T(Ta) wave and atrial gradient in patients with A-V block

Hiroshi Hayashi M D *
Mitsuharu Okajima M D **
Kazuo Yamada M D ***
Nagoya Japan

The Ta wave represents the recovery process of the electrical excitation in the atrium The Ta wave is usually hard to recognize because (1) the amplitude of the Ta wave is very small and (2) it merges mostly with the QRS complex in normal conditions The Ta wave is important however as a diagnostic clue for atrial infarction or injury Furthermore there is a danger of it leading to an erroneous diagnosis of coronary insufficiency or myocardial damage because it may cause false depression of the ST segment

There are some experimental [2] and clinical studies [7] on the Ta wave but the studies are small in number compared to those of ventricular properties Previously we reported on the Ta loop with and without atrial injury in dog experiments and the Ta loop in clinical cases was also studied In the work reported in the present paper the Ta waves were investigated in electrocardiograms (ECG) of patients with A V block by means of high speed and high amplification recording techniques

Materials and methods

Twenty five patients with A V block of various degrees were divided into two groups (Table I) Group A consisted of 20 patients with only slight subjective symptoms and no significant cardiovascular diseases by history except mild hypertension or left ventricular hypertrophy In standard ECG records abnormalities of the P wave were not observed in this group Group B consisted of five patients with severe cardiovascular diseases Ages in Group A ranged from 13 to 74 years and those in Group B from 18 to 69 Standard 12 lead ECG s of these two groups were recorded at the sensitivity of 100 μV = 3 cm and at a paper speed of 10 cm per second The recording equipment employed has been reported in recent papers [13,14] The transitional point between the P and the Ta waves was arbitrarily determined as the point where the deflection of the P wave crosses the isoelectric line and moves to the gently curved Ta wave The Ta maximum time represents the time from the beginning of the P wave to the point where the Ta wave has the largest amplitude The measurement of the atrial gradient has been described elsewhere [3]

Results

Case 1 In the standard ECG of a 26 year old woman (Group A) the P wave was followed by a gently curved wave which was opposite in direction to the P wave in every lead (Fig 1) In a high speed magnified ECG the P wave showed a tall and sharp spike followed by the Ta wave which was drawn gently like a dish or a dome with the polarity opposite to the P wave in each lead (Fig 2)

Case 29 In the standard ECG of a 67 year old man (Group B) a slight deflection could be observed following the P wave in each lead (Fig 3) In a magnified ECG the P wave was small and notched in many leads (Fig 4) It lost the sharp

From the Circulation and Respiration Division Research Institute of Environmental Medicine Nagoya University Nagoya, Japan
Received for publication April 24 1975
Reprint requests Hiroshi Hayashi, M D Emory University School of Medicine Internal Medicine Cardiology 69 Butler St., S E Atlanta Ga. 30303.

Research Associate Cardiovascular Research and Training Institute College of Medicine University of Utah Salt Lake City Utah 84132.

Professor of Medicine College of Medicine Fujita-Gakuen University Toyoake Japan.

Professor the Circulation and Respiration Division Research Institute of Environmental Medicine Nagoya University Nagoya Japan.

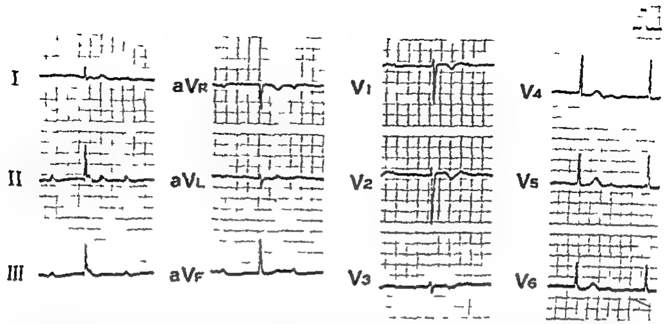

Fig 1 A 26 year old woman (Group A) She had no significant complaints Complete A V block was observed In each lead the P wave is followed by a gentle deflection in the opposite direction (Ta wave) The ST depression seen in Leads II III and V is due to the Ta deflection (Case No 1 calibration = 1 mV)

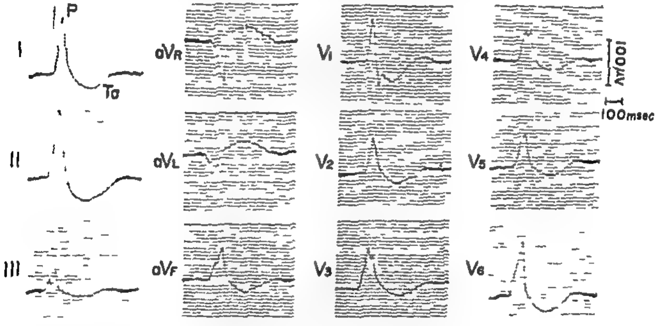

Fig 2 The same case as in Fig 1 recorded by high speed magnified electrocardiography The P and the Ta waves are recorded in the opposite direction to each other in each lead

contour and was rounded on its summit The Ta wave was relatively large compared with the P wave It was not inscribed in the opposite direction to the P wave in most leads

Configuration and polarity of the Ta wave In Group A patients the P wave was rather sharp like a spike and the Ta wave was gently curved like a dish or dome The P wave had no significant notches and the Ta wave was smooth in configuration without any angle The Ta wave showed a sharp or large arc when the P wave was large and a gentle or small arc when the P wave was rather small When the P wave was diphasic initially positive and then negative, as in V_1 the Ta wave also formed two gentle phases initially negative and then positive The Ta wave was usually negative in Leads I II, III aV_L, aV_F and V_{2-6} and positive in aV_R The Ta wave was always opposite in direction to the P wave

In Group B the P wave either had prominent

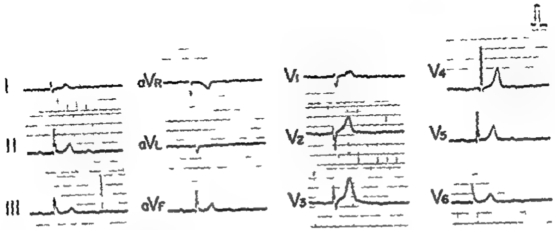

Fig 3 A 67 year-old man (Group B) He suffered frequent anginal attacks and complete A V block for 4 years In each lead the P wave is followed by a gentle deflection (Ta wave) (Case No 29 calibration = 1 mV)

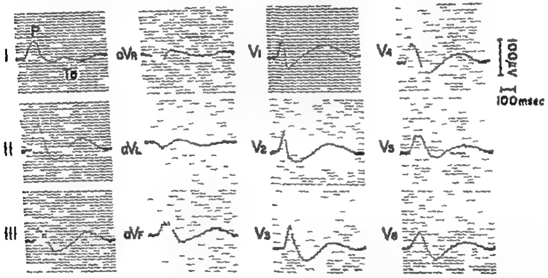

Fig 4 The same case as in Fig 3 recorded by high-speed magnified electrocardiography The P wave is small in all leads and loses the sharpness on top The Ta wave is diphasic in all leads and its main deflection is the same polarity as the P wave The amplitude of the Ta wave is comparable to that of the P wave in each lead.

notches or lost the sharpness and became rounded on top of the wave (Fig 5) The Ta wave also lost the smoothness becoming angulated or uneven The relative amplitude of the Ta wave became abnormally large or conversely very small compared with the P wave In some leads the initial part of the Ta wave was opposite in direction to the P wave and later moved in the same direction as the P wave although the P wave was not diphasic

Amplitude of the Ta wave The Ta wave amplitude in the precordial leads was generally large in Group A (Table II) An obvious positive correlation was observed between the amplitude of the Ta and the P waves in every lead it was described by the equation

$$-Ta = 0.25\ P + 5\ (\mu V)\ (\text{Lead II})\ (\text{Fig } 6)$$

The ratio of amplitude of the Ta and the P waves (Ta/P) was 0.38 on the average

In Group B the amplitude of the Ta wave showed great variability being as large as 86 μV in Lead I The amplitude of the P wave did not differ as much from that in Group A There was no clear

Table I Subjects used in this study

Case No	Patient	Age	Sex	Degree of A V block	Clinical symptoms and findings
Group A					
1	Y O	26	F	3	Palpitation shortness of breath
2	H M	61	M	3	None
4	Z K	73	M	3	None
5	H Y	69	F	3	None
6	H Y	27	F	1	PQ = 0 36 sec
7	H U	61	F	3	None
8	H O	60	M	1	Hypertension (172/98) PQ = 0 37 sec
9	T T	51	F	1	Hypertension (190/110) PQ = 0 38 sec
10	J M	13	M	1	None
12	K I	74	M	3	Hypertension (170/80) palpitation
13	T H	16	M	3	None
14	Y O	59	M	3	Hypertension (165/85) palpitation shortness of breath
15	T S	70	M	3	Shortness of breath
16	T G	42	M	3	None
17	K M	49	F	3	Shortness of breath
19	M H	63	F	3	Shortness of breath
23	K Y	64	F	2	Hypertension (176/98) LVH shortness of breath
24	A Y	40	M	1	Shortness of breath on exercise PQ = 0 38 sec
27	Z M	62	M	2	Minor angina pectoris 2 yr ago
28	T K	42	M	3	None
Group B					
3	T O	55	M	3	Posterior inferior myocardial infarction 3 yr ago
11	R O	18	M	3	Aortic insufficiency mitral insufficiency
18	T K	69	F	3	RBBB arteriosclerosis
25	K M	47	M	3	Hypertension (172/100) arteriosclerosis fainting attacks abnormal ST T transient hemiplegia 2 yr ago
29	T S	67	M	3	Arteriosclerosis frequent attacks of angina pectoris for 4 yr fainting attacks

relationship between the amplitude of both waves in any lead, Ta/P ratio ranging from 0 14 to as large as 0 86 (Fig 4)

Duration of the Ta wave The mean duration of the Ta wave in Group A was 276 msec in Lead II (Table II) The mean Ta/P ratio of duration was 2 7 in Lead II

Table II Comparison of values cases in human subjects (Group A) and dogs without atrial injury

	Human (Group A) Mean	Human (Group A) Maximum	Human (Group A) Minimum	Normal dog Mean	Normal dog Maximum	Normal dog Minimum
Amplitude of Ta (μV)						
aVF	20	40	8	33	53	13
V_1	30	69	22	27	41	19
V_5	27	50	14	31	55	14
Amplitude of P (μV)						
aVF	59	123	25	178	251	109
V_1	87	135	52	83	108	60
V	69	136	35	126	279	41
Ta/P ratio of amplitude	0 38	0 45	0 22	0 24	0 32	0 18
Relationship of amplitude between P and Ta	−Ta = 0 25 P + 5 (μV)			−Ta = 0 19 P + 8 (μV)		
Duration of Ta (msec) (Lead II)	276	315	230	148	191	11[illegible]
Duration of P (msec) (Lead II)	104	120	88	63	87	[illegible]
Ta/P ratio of duration (Lead II)	2 7	3 4	2 3	2 2	3 4	1 6
P + Ta time (msec) (Lead II)	396	458	330	217	263	179
Ta maximum time (msec)	219	268	190	145	161	130
Relationship between P + Ta time and P P interval	P + Ta = 0 25 (P P) + 172 (msec)			P + Ta = 0 29 (P P) + 87 (msec)		
Component of atrial gradient (μV sec)†						
aVF	0 8	1 8	−1 8	0 5	1 5	−0 7
V	1 0	4 3	−2 0	0 5	0 8	0 1
V	0 7	2 8	−1 4	0 4	0 7	0 2

Amplitude of P and Ta wave in absolute value
†Mean values of component of atrial gradient in absolute value

The duration of the Ta wave in Group B ranged from 242 to 384 msec and that of the P wave from 93 to 120 msec The Ta/P ratio of the duration ranged from 2 2 to 3 3, mean value being 2 7 in Group B

P+Ta time and Ta maximum time In Group A the P+Ta time was 386 msec and the Ta maximum time was on the average 219 msec in Lead II (Table II) In Group B the P+Ta time was remarkably prolonged in one case (502 msec) compared with that in Group A The Ta maximum time in Group B was markedly prolonged in two cases and shortened in two cases

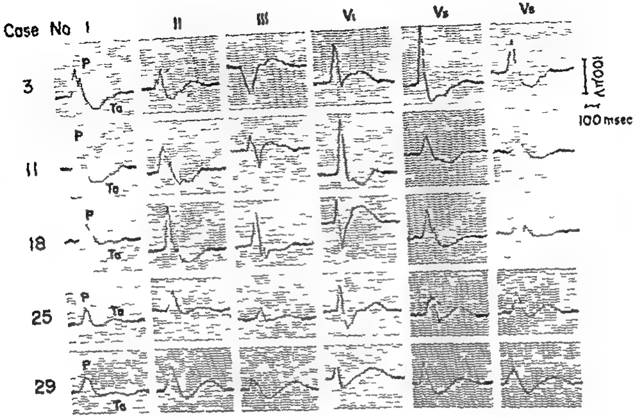

Fig 5 The P and the Ta waves in Group B

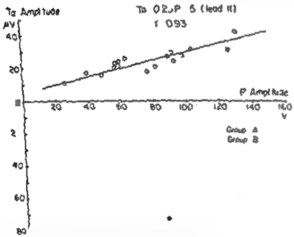

Fig 6 There is a positive correlation between the amplitude of the P and the Ta waves in Group A No close relationship exists between the two in Group B

An obvious positive correlation was observed between the P+Ta time and the P P interval in Group A (Fig 7) It was described by the equation

$$P+Ta = 0\,25\,(P\,P) + 1.\quad (msec)$$

Table III Component of atrial gradient in each lead (μV sec) Mean value in group A is shown in absolute value

ECG lead	Group A Mean	Group A Maximum	Group A Minimum	Group B Maximum	Group B Minimum
I	07	04	−1 2	1.3	−1.8
II	07	1 4	−1 2	3.5	−1 3
III	1 3	2 6	−3 3	0.2	−0.5
aV_R	1 1	1 7	−1 9	1 9	−2 4
aV_L	1 0	2 0	−1 4	3 4	−1.5
aV_F	08	1.8	−1 8	4 6	−0 5
V	1 0	4 3	−?0	9 6	−2 8
V	1 4	4.3	−4 1	3 1	−2 3
V	08	09	−1 7	4 8	−4 0
V	09	2 7	−1 4	?6	−3.5
V	07	2.8	−1 4	3 6	−1.9
V	08	1 9	−1 7	3.2	−1.8

Absolute value

All five cases in Group B showed a correlation similar to that in Group A

Atrial gradient The components of the atrial gradient in Leads aV_F, V_1 and V_5 are shown in Table III They were relatively small in Group A

Table I Subjects used in this study

Case No	*Patient*	*Age*	*Sex*	*Degree of A V block*	*Clinical symptoms and findings*
Group A					
1	Y O	26	F	3	Palpitation shortness of breath
2	H M	61	M	3	None
4	Z K	73	M	3	None
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7	H U	61	F	3	None
8	H O	60	M	1	Hypertension (172/99) PQ = 0 37 sec
9	T T	51	F	1	Hypertension (190/110) PQ = 0 38 sec
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15	T S	70	M	3	Shortness of breath
16	T G	42	M	3	None
17	K M	49	F	3	Shortness of breath
19	M H	63	F	3	Shortness of breath
23	K Y	64	F	2	Hypertension (176/99) LVH shortness of breath
24	A Y	40	M	1	Shortness of breath on exercise PQ = 0 39 sec
27	Z M	62	M	2	Minor angina pectoris 2 yr ago
28	F K	42	M	3	None
Group B					
3	T O	55	M	3	Posterior inferior myocardial infarction 3 yr ago
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18	T K	69	F	3	RBBB arteriosclerosis
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relationship between the amplitude of both waves in any lead Ta/P ratio ranging from 0 14 to as large as 0 86 (Fig 4)

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Table II Comparison of values cases in human subjects (Group A) and dogs without atrial injury

	Human (Group A)			*Normal dog*		
	Mean	*Maximum*	*Minimum*	*Mean*	*Maximum*	*Minimum*
Amplitude of Ta (μV)						
aV_F	20	40	8	33	53	13
V	30	69	22	27	41	19
V,	27	50	14	31	55	14
Amplitude of P (μV)						
aV_F	59	123	25	178	251	109
V	87	135	52	63	108	60
V,	89	136	35	126	279	41
Ta/P ratio of amplitude	0 38	0 45	0 22	0 24	0 32	0 18
Relationship of amplitude between P and Ta	−Ta = 0 25 P + 5 (μV)			−Ta = 0 19 P + 8 (μV)		
Duration of Ta (msec) (Lead II)	276	315	230	148	191	117
Duration of P (msec) (Lead II)	104	120	88	69	87	60
Ta/P ratio of duration (Lead II)	2 7	3 4	2 3	2 2	3 4	1 6
P + Ta time (msec) (Lead II)	386	458	330	217	263	179
Ta maximum time (msec)	219	268	190	145	161	130
Relationship between P + Ta time and P P interval	P + Ta = 0 25 (P P) + 172 (msec)			P + Ta = 0 29 (P P) + 87 (msec)		
Component of atrial gradient (μV sec)†						
aV_F	0 8	1 8	−1 8	0 5	1 5	−0 7
V	1 0	4 3	−2 0	0 5	0 8	0 1
V	0 7	2 8	−1 4	0 4	0 7	0 0

Amplitude of P and Ta wave in absolute value
†Mean values of component of atrial gradient in absolute value

The duration of the Ta wave in *Group B* ranged from 212 to 384 msec and that of the P wave from 93 to 120 msec The Ta/P ratio of the duration ranged from 2 2 to 3 3 mean value being 2 7 in Group B

P+Ta time and Ta maximum time In Group A the P+Ta time was 386 msec and the Ta maximum time was on the average 219 msec in Lead II (Table II) In Group B the P+Ta time was remarkably prolonged in one case (502 msec) compared with that in Group A The Ta maximum time in *Group B* was markedly prolonged in two cases and shortened in two cases

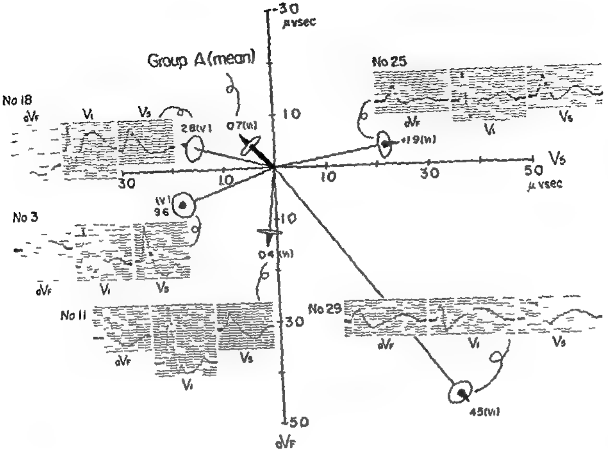

Fig 8 The spatial atrial gradient in Group A (mean value) and Group B The magnitude of the anterior posterior direction (V) of the vector is indicated in the parentheses and by the shape of the arrow

small range prior to atrial injury being 0 24 on the average After atrial injury was produced the ratio varied a great deal ranging from 0 12 to 0 96

In routine standard ECG s it can be seen that the PQ segment deviates to the opposite direction of the P wave in most cases If PQ segment deviation is greater than expected from the amplitude of the P wave or if it is on the isoelectric line or deviated in the same direction as the P wave in routine clinical ECG a careful attention should be given to the possibility of atrial pathology

Fig 9 shows the PQ segment displacement found in a routine clinical ECG The patient a 62 year old man suffered a posterior inferior myocardial infarction 1 year prior to this recording He had been doing well after the attack without significant complaint On Dec 3 1968 he complained of chest distress In the ECG the PQ segment merged into the QRS complex without returning to the isoelectric line with the P wave and PQ segment being of the same polarity in V_1 This finding was emphasized after an exercise test The same findings were observed in V_4 and V About 1 month later the PQ segment returned to below the isoelectric line opposite in direction to the P wave in both rest and exercise ECG s By this time the patient s complaint had cleared This case might suggest an episode of atrial injury or infarction and its recovery

Though reports on the duration of the Ta wave are few the Ta/P ratio of duration has been reported as 2 7 [3] 3 7 and 4 0 [4] in clinical cases The latter two are large and comparable to those in Group B in the present study There are some reports on P+Ta time in the past which varied from 150 to 600 msec [2 ... 12] Those cases in which the duration was very long in past studies might be similar to those in Group B in our study

The P+Ta time far exceeds the QRS complex in the ECG and the Ta wave has influence on the ST segment When the P wave is positive the Ta

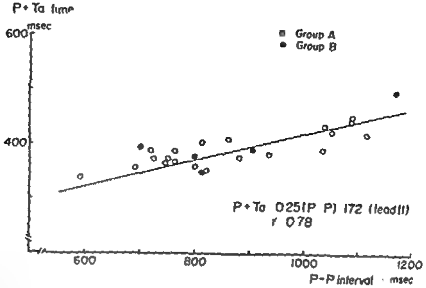

Fig 7 The relationship between the P+Ta time and the P P interval There is a positive correlation in Group A and Group B shows a similar one

with a mean value of less than 1 0 μVsec In Group B the value in Lead V, was especially large In 13 of 20 cases in Group A the components of atrial gradient in Leads aV, V, and V, showed a negative value The spatial atrial gradient based on the average of these 13 cases was oriented to the right, superiorly and posteriorly, the magnitude being 1 2 μVsec (Fig 8) The spatial atrial gradient in Group B is shown in the same figure The magnitude was 9 8 μVsec (case 3) 1 6 μVsec (case 11) 3 4 μVsec (case 18) 3 1 μVsec (case 25) and 7 4 μVsec (case 29) The direction of the vector was rightward inferior and anterior (case 3) rightward, inferior and posterior (case 11) rightward superior and posterior (case 18) leftward superior and anterior (case 25), and leftward, inferior and anterior (case 29)

Discussion

Since Kraus and Nicolai[16] Samojiloff[17] and Straub[1] described the after wave following the P wave considerable numbers of experimental or clinical studies were done by Hering[1] and by Abramson and co workers[18]

Due to the number of limitations such as difficult recognition of the Ta wave and the technical problems of the experiment, the Ta wave has not yet been fully clarified We have previously performed an experimental study on dogs to investigate normal and abnormal Ta waves[15]

The P Ta segments which were described by Abramson[18] and Tranchesi[12] did not exist between the P and the Ta waves in either normal or abnormal states in our study This may be attributed to the fact that the duration of the action potential of the atrium is short compared with that of the ventricle and there is almost no plateau phase in the membrane action potential or, if any a very short one[20] Consequently the repolarization process starts immediately after the depolarization process and continues throughout the PQ interval This has been clearly shown by Spach and associates[4] in their study of electrical potential distribution surrounding the atria The Ta wave in our dog experiments[15] without atrial injury showed a similarity to that of the human subjects in Group A with respect to the shape and polarity and the relationship with the P wave (Table II) After atrial injury was produced in the dog changes in the Ta wave similar to those seen in the human patients of Group B were observed This observation raises the possibility that those in Group B might have some injury in the atria These abnormalities of the Ta wave were frequently observed without any accompanying abnormalities of the P wave Thus the Ta wave might give us an important clue to find the existence of disease in the atria In Group A the amplitude of the Ta wave was in direct proportion to that of the P wave Wasserburger and associates[11] also reported that there was a correlation between the depression of the Ta wave and the amplitude of the P wave In Group B, however, there was no specific relationship between the two waves the Ta/P ratio being very large in some and very small in the others In the dog experiments the Ta/P ratio was within a

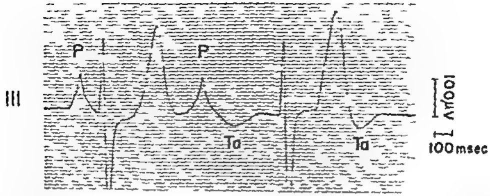

Fig 10 *The false depression of the ST segment due to the Ta wave The case shows complete A V block with positive P wave and negative Ta wave The P wave is inscribed immediately before the first QRS complex and the Ta wave overlaps the ST segment causing the depression of the segment It can be judged from the normal ST segment in the second QRS T segment that the ST depression in this case is caused by the Ta wave*

icant This may be due in part to the fact that the symptoms of atrial infarction were slight compared to those of ventricular infarction and those clinical pictures were masked by the frequently accompanying ventricular infarction which showed dramatic clinical features Atrial infarction is not necessarily rare[33,36] however nor negligibly mild in symptoms[35,37,36] There are several reports of atrial infarction with or without association with ventricular infarction[31,32,33,37]

It is hoped that careful attention to the Ta wave would serve in the early detection of transient or reversible pathophysiologic changes in the atria which may or may not be related to the ventricular pathologic changes

Summary

The P and the Ta waves of two patient groups with A V block were magnified with a direct current amplifier and recorded at a high paper speed

In Group A patients (those without serious cardiovascular complications except A V block) the P and the Ta waves were recorded in the opposite direction in every lead and there was a linear relationship between the amplitude of the P and the Ta waves The atrial gradient was nearly zero There existed a positive correlation between the P + Ta time and the P P interval

In Group B patients (those with serious cardiovascular complications besides A V block) there were significant differences in the Ta wave from Group A with respect to form polarity amplitude duration and the relationship between the Ta and the P waves The atrial gradient was markedly large

Careful attention should be paid to the deviation of the PQ segment caused by the Ta wave in daily ECG s to detect atrial abnormalities

The Ta wave extends into the ST segment and while describing the deviation of the ST segment the influence of the Ta wave should be kept in mind

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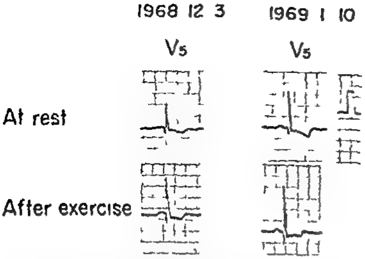

Fig 9 A 62 year old man The PQ segment is displaced in the same direction as the P wave both in rest and exercise ECG's (left) About 1 month later the PQ segment has returned to below the isoelectric line and his complaint has disappeared by then

wave is inscribed in a negative direction When the Ta wave is large it might cause false ST depression and lead to an erroneous diagnosis of myocardial injury (Fig 10) The maximum Ta time falls on the latter part of the P + Ta time and its influence on the ST segment is more pronounced

There was a linear relationship between P+Ta time and P P interval in Group A Kesselman and associates[7] also gave an equation similar to ours

$$P+Ta = 0.34\,(P\text{-}P) + 140$$

In this manner an approximate value of the P+Ta time may be estimated from P P interval The amplitude of the Ta wave can also be estimated from that of the P wave The influence of the Ta wave on the ST segment can be estimated rather quantitatively It is quite reasonable that the American Heart Association recognized the problem and to avoid the influence of the Ta wave on the ST segment recommended using the junction of the PR segment and the QRS complex as a baseline when the ST deviation is judged[2] If the Ta wave is inscribed in the same direction as the P wave as in cases of atrial injury as shown in the experimental study by the authors[15] it is adequate to use the T-P line or U P line as a baseline

In normal cases the P and the Ta waves were recorded in the opposite direction in every lead This may suggest that in the atrium, in contrast to the ventricle the direction of depolarization and repolarization is the same as in single cardiac muscle fiber This may be attributed the facts that (1) the intra atrial pressure is not so high as that of the ventricle[9] and (2) as the atrial muscle is very thin there is almost no difference in temperature between the endocardium and the epicardium[3] In other words there are few factors that will make an atrial gradient In Group B patients the P and the Ta waves were inscribed in the same direction in some cases This indicates that the direction of depolarization and repolarization changed becoming the opposite of each other thereby suggesting the existence of atrial injury, which has been proved in the dog experiment[15] In the present study the atrial gradient was close to zero but not exactly zero The reason may be that the manner of excitation and recovery varies from site to site in the atria i e the difference in the form and/or the duration of the membrane action potential Since Wilson and associates[4] advocated the concept of ventricular gradient many investigators have studied this problem qualitatively and quantitatively and this concept has been applied also to the atrium Thereafter Lepeschkin[1] and Berkun and associates[10] reported that the P and the Ta waves were opposite in direction and the area of each wave was almost equal the atrial gradient being nearly zero in the normal heart In the former studies both P and Ta waves were very small in amplitude and there was a question about accuracy In the present study both waves were recorded in large amplitude and very reliable results were expected The results should be considered to show that the direction of depolarization and repolarization is the same and there is not much local difference in the time sequences between the activation sequence and the recovery one

On the other hand both the atrial gradient component in each lead and the spatial atrial gradient in Group B patients were markedly large The direction of the latter varied from case to case We have shown in the dog experiment that the direction of the spatial atrial gradient pointed to the site of atrial injury If this fact can safely be applied to cases in human subjects it would be possible to determine the injury site as well as the existence of atrial injury or strain It has been supposed that atrial infarction was a rare condition and the clinical value was insignif

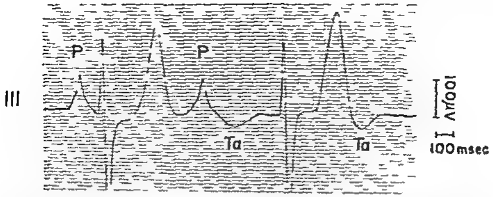

Fig 10 The false depression of the ST segment due to the Ta wave The case shows complete A V block with positive P wave and negative Ta wave The P wave is inscribed immediately before the first QRS complex and the Ta wave overlaps the ST segment causing the depression of the segment It can be judged from the normal ST segment in the second QRS T segment that the ST depression in this case is caused by the Ta wave

icant This may be due in part to the fact that the symptoms of atrial infarction were slight compared to those of ventricular infarction and those clinical pictures were masked by the frequently accompanying ventricular infarction which showed dramatic clinical features Atrial infarction is not necessarily rare[23] however nor negligibly mild in symptoms[37] There are several reports of atrial infarction with or without association with ventricular infarction[1 32 3 37]

It is hoped that careful attention to the Ta wave would serve in the early detection of transient or reversible pathophysiologic changes in the atria which may or may not be related to the ventricular pathologic changes

Summary

The P and the Ta waves of two patient groups with A V block were magnified with a direct current amplifier and recorded at a high paper speed

In Group A patients (those without serious cardiovascular complications except A V block) the P and the Ta waves were recorded in the opposite direction in every lead and there was a linear relationship between the amplitude of the P and the Ta waves The atrial gradient was nearly zero There existed a positive correlation between the P + Ta time and the P P interval

In Group B patients (those with serious cardiovascular complications besides A V block) there were significant differences in the Ta wave from Group A with respect to form polarity amplitude duration and the relationship between the Ta and the P waves The atrial gradient was markedly large

Careful attention should be paid to the deviation of the PQ segment caused by the Ta wave in daily ECG s to detect atrial abnormalities

The Ta wave extends into the ST segment and while describing the deviation of the ST segment the influence of the Ta wave should be kept in mind

The authors wish to express their appreciation to Dr G Michael Vincent for his constructive comments criticism and valuable help in English.

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Vectorcardiographic, electrocardiographic, and angiographic correlations in apparently isolated inferior wall myocardial infarction

Jawahar Mehta, M.D.
Irwin Hoffman, M.D.
P. Smedresman, M.D.
Joseph Hilsenrath, M.D.
Robert I. Hamby, M.D.
New Hyde Park and Stony Brook, N. Y.

Left ventricular function as measured by left ventriculography and hemodynamics is more frequently impaired when the electrocardiogram (ECG) indicates anterior wall myocardial infarction than is the case with inferior infarction patterns.[1] Indeed, in a study of 264 patients[2] it was concluded that anterior or anterior plus inferior infarction patterns correlated with poor left ventricular function because these two groups share anterior wall damage. When the "isolated" inferior infarction group was closely examined, it became evident that although the mean values for ejection fraction and end-diastolic volume were normal, a large scatter was evident, with many values clearly falling in the abnormal range. It was also observed that 25 per cent of the patients in this group had unexpected asynergy of the anterior or apical wall of the left ventricle.

A study was therefore designed to determine if the patients with ECG evidence of "isolated" inferior infarction but with poor left ventricular ejection also demonstrated dysfunction of the anterior wall on left ventricular angiography and further, if such dysfunction was detectable with vectorcardiography (VCG).

From the Department of Medicine, Division of Cardiology, Long Island Jewish-Hillside Medical Center, New Hyde Park, N. Y., and School of Medicine, State University of New York, Stony Brook, N. Y.

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Reprint requests: Jawahar Mehta, M.D., Division of Cardiology, School of Medicine, University of Minnesota, Minneapolis, Minn.

Materials and Methods

We compared a group of 26 patients who had isolated transmural inferior myocardial infarction patterns on ECG and abnormal ejection fractions with another group of 26 patients who had similar inferior wall infarctions but normal left ventricular ejection fractions. These 52 patients were selected from a group of 435 with chest pain who underwent coronary arteriography and left ventricular angiography at the Long Island Jewish-Hillside Medical Center. Twelve lead ECG's were performed with a Marquette Series 3000 machine operated at a paper speed of 25 mm. per second and standardization adjusted to 1 cm. per millivolt. Tracings demonstrating anterior, posterior, or lateral wall infarction, left or right bundle branch block, left anterior or posterior hemiblock, left or right ventricular hypertrophy, or artificial cardiac pacing were excluded from the study.

All patients had a chest x-ray interpreted by a radiologist to define the presence or absence of cardiomegaly. Frank VCG's, available on 35 patients, were interpreted according to accepted criteria.[3,4] VCG's were recorded with a Hewlett Packard/Sanborn vector amplifier and Visoscope Model No. 569A. Loops were photographed with Polaroid high speed film. The usual magnification employed was 1 mV. = 5 cm.

Left ventricular angiograms were obtained in the right anterior oblique projection by injecting 0.50 to 0.75 ml. per kilogram of 75 per cent sodium

Table I Left ventricular contractile pattern in isolated inferior infarction

	Ejection fraction		Asynergy			
	Range	Mean ± 1 S D	Inferior	Anterior	Apical	Generalized hypokinesia
Group A (EF < 50%) n = 26	16 49	39 ± 9 59	23	10	7	2
Group B (EF > 50%) n = 26	51 75	62 ± 6 58	17	3	2	0

meglumine diatrizoate through either the retrograde or transseptal catheter Cineangiograms were taken with a 35 mm camera at a rate of 60 frames per second After the completion of the left ventricular injection selective coronary angiograms were performed in multiple projections according to methods described by Sones and Shirey[1] or Judkins[11] The pattern of left ventricular contraction was determined by superimposition of the end diastolic and end systolic silhouettes as defined by Herman and associates[1] Left ventricular volumes were obtained by using a modification of the area length method[1] and the regression equation derived by Hermann and Bartle[11] By this method the ejection fraction was determined in each patient Significant disease of a coronary artery was assumed if the lumen was occluded 50 per cent or more[1] Obstruction in each of the three main coronary arteries and the left main coronary artery was graded from 0 to 6 depending on the severity of obstruction as defined by Bruschke[13] ECG VCG and angiographic data were analyzed by separate observers

Results

Twenty six patients with inferior infarction patterns (ECG) and poor ejection fractions (Group A) were compared with 26 patients with similar inferior infarction patterns and good ejection fractions (Group B) There were 25 males and one female in each group The mean age for the two groups was identical (52 ± 7 years in Group A and 52 ± 5 years in Group B) Cardiomegaly was present in eight patients in Group A whereas none of the patients in Group B had any evidence of cardiac enlargement

Left ventricular contractile patterns and coronary disease Table I lists the left ventricular contractile patterns in the two groups Sixty three per cent of the patients with poor ejection fractions (EF) associated with inferior infarction (Group A) had evidence of asynergy of the anterior and/or apical wall of the left ventricle in addition to the expected inferoposterior asynergy Two patients had generalized hypokinesia

Twenty three of the 26 patients had the expected asynergy of the inferior wall In comparison fewer patients in Group B had involvement beyond the inferoposterior wall (anterior 3 and apical 2) One patient in Group A had moderate mitral insufficiency as well The mean ejection fractions in the two groups were 39 ± 9 59 and 62 ± 6 58 per cent respectively

Mean coronary scores for each artery in the two groups are shown in Table II The severity of right coronary artery disease was identical in both groups whereas Group A manifested greater involvement of the circumflex (3 50 ± 1 72 vs 2 10 ± 1 74) and left anterior descending (3 96 ± 1 48 vs 2 78 ± 1 60) arteries The numbers of vessels involved with significant disease were different in the two groups (Table II) The frequency of triple vessel disease in Group A was 65 per cent (17 of 26 patients) compared to only 32 per cent (eight patients) in Group B Single vessel disease only (right coronary or dominant circumflex artery) was present in only one patient of Group A but in nine of Group B One patient in Group B had no significant disease in any of the coronary arteries yet had evidence of inferior infarction on the ECG

Vectrocardiographic correlations VCG s were available in 18 patients in Group A and 17 patients in Group B These were correlated with the catheterization data The results of VCG interpretation are shown in Table III All patients showed evidence of inferior infarction confirming the ECG s VCG evidence of posterior wall (dorsal) infarction was present in three patients in each group All six manifested asynergy of the inferodorsal wall of the left ventricle as seen on the left ventricular angiograms Evidence of anterior infarction was found in five patients in Group A (28 per cent) but in

Table II Results of coronary arteriography in isolated inferior infarction

	Coronary scores (mean)				No of vessels involved			
	MLC	LCx	RCA	LAD	None	Single	Double	Triple
Group A (EF < 50%) (n = 26)	0.37 ± 0.88	3.50 ± 1.72	4.40 ± 1.25	3.96 ± 1.48	0	1	8	17
Group B (EF > 50%) n = 26	0.10 ± 0.41	2.10 ± 1.74	4.40 ± 1.50	2.78 ± 1.50	1	9	8	8

MLC Main left coronary artery LCx left circumflex artery RCA right coronary artery LAD left anterior descending artery

Table III ECG VCG arteriographic and ventriculographic correlations

No	ECG	VCG	Coronary artery disease			Asynergy			EF (%)
			LAD	RCA	Cx	Inferior	Anterior	Apical	
Group A									
1	IMI	IMI + AMI	+	+	+	+	0	+	44
2	IMI	IMI + AMI	+	+	0	+	+	0	45
3	IMI	IMI + AMI + LAHB	+	+	+	+	+	0	49
4	IMI	IMI + AMI	+	+	+	+	+	0	43
5	IMI	IMI + AMI	+	+	+	0	+	+	32
6	IMI	IMI	+	+	+	0	0	+	47
7	IMI	IMI	+	+	+	+	0	0	46
8	IMI	IMI	0	+	0	+	0	0	48
9	IMI	IMI	+	+	+	+	0	+	43
10	IMI	IMI + LVH	+	+	+	+	0	+	22
11	IMI	IMI	+	+	+	+	0	0	16
12	IMI	IMI	+	+	0	+	+	0	47
13	IMI	IMI	+	+	+	+	0	0	43
14	IMI	IMI + DMI	+	+	+	+	+	0	26
15	IMI	IMI + DMI + LVH	+	+	0	+	+	0	38
16	IMI	IMI+LVH	+	+	0	+	0	+	38
17	IMI	IMI + DMI	+	0	+	+	0	0	45
18	IMI	IMI	+	+	+	+	0	0	46
Group B									
1	IMI	IMI + DMI	+	+	0	+	0	0	64
2	IMI	IMI	+	+	+	+	0	0	64
3	IMI	IMI	+	+	+	+	0	+	53
4	IMI	IMI	+	+	0	+	0	0	51
5	IMI	IMI	0	+	0	+	0	0	60
6	IMI	IMI	0	0	0	+	0	0	75
7	IMI	IMI	0	+	0	+	0	0	66
8	IMI	IMI + LVH	+	+	0	+	0	0	63
9	IMI	IMI + DMI	0	+	0	+	0	0	66
10	IMI	IMI	+	+	+	+	0	0	60
11	IMI	IMI + AMI	+	+	0	+	+	0	5[illegible]
12	IMI	IMI	+	+	+	+	0	0	52
13	IMI	IMI	0	+	0	+	0	0	55
14	IMI	IMI + DMI	0	+	0	+	0	0	67
15	IMI	IMI	+	0	+	0	0	0	66
16	IMI	IMI	0	+	0	+	0	0	59
17	IMI	IMI	+	+	+	+	0	0	45

IMI Inferior wall myocardial infarction DMI dorsal wall myocardial infarction AMI, anterior wall myocardial infarction LVH left ventricular hypertrophy LAHB left anterior hemi-block

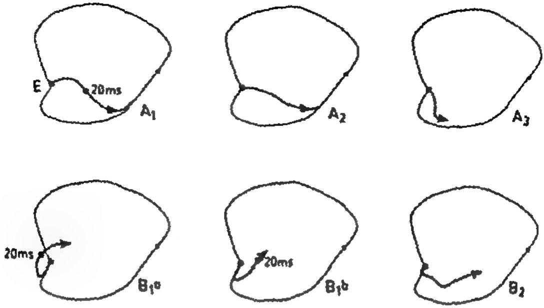

Fig 1 *Criteria for anteroseptal infarction* (A_1) Initial part of the vector loop takes a leftward and posterior course In isolated anteroseptal infarction the 20 msec vector should return to a point anterior to E (A_2) The initial part although anterior to E recedes to the left This may result in a flat concavity (A_3) Circumscript concavity from the right and anterior during the initial 15 msec *Criteria for strictly anterior infarction* (B_1) Following the forward septal activity the centrifugal part of the loop turns immediately to posterior and the 20 msec vector has a posterior direction This is manifested in two ways in the horizontal projection In B_1a the centrifugal part runs a clockwise course behind the point E and in B_1b the centrifugal part follows a counterclockwise course in front of E (B_2) A concavity from anterior occurring after 15 to 30 msec (Adapted from Van Herpen G Bruschke A V G and Hansen A W In Proceedings of the XI International Vectorcardiography Symposium Published by North Holland Publishing Company)

Table IV Summary of VCG findings in 35 patients with inferior infarction

	IMI	*AMI*	*DMI*	*LVH*	*LAHB**
EF < 50% n = 18	18	5	3	3	1
EF ≥ 50% n = 17	17	1	3	1	0

LAHB Left anterior hemiblock

only one patient of Group B (6 per cent) These six patients had anterior and/or apical asynergy by left ventriculography The VCG s also revealed left anterior hemiblock in one patient and left ventricular hypertrophy in three patients in Group A In contrast, left ventricular hypertrophy was present in only one patient in Group B and none had left anterior hemiblock These results are summarized in Table IV

Discussion

The classic VCG abnormality in anterior wall myocardial infarction consists of a posterior horizontal loop with clockwise rotation and very small or absent anterior initial QRS forces [8] This picture has recently been correlated with extensive anterior wall asynergy [18] The present study addresses itself to more subtle VCG residuals of anterior wall disease which are insufficient in themselves to eliminate precordial unipolar R waves or to change the major rotation of the horizontal QRS loop

In this study all the 35 frontal plane VCG s exhibited leftward QRS loops with clockwise movement and with the 30 msec vector superior to the X axis, meeting accepted criteria for inferior wall myocardial infarction The VCG criteria that we accepted as evidence for anterior wall myocardial infarction are summarized in Fig 1

In five of 18 patients with unequivocal ECG evidence of inferior infarction and poor ejection fractions one or more of these criteria were satisfied In four of the five cases anterior asynergy was observed, apical asynergy was present in the fifth Three additional patients in this group had anterior and four had apical asynergy but none of these seven satisfied criteria for anterior wall infarction by VCG Thus of all 12 patients with inferior infarction poor ejection

fraction and anterior asynergy VCG correctly identified five (42 per cent)

In addition to detection of unsuspected anterior infarction vectorcardiography proved of additional value in the poor ejection fraction group in the diagnosis of dorsal wall infarction in three left ventricular hypertrophy in three and left anterior hemiblock in one patient

In sharp contrast stand the 17 patients with inferior wall infarction and normal ejection fractions Only two had anterior or apical asynergy and only one of these met VCG criteria for anterior myocardial infarction It seems clear from these results that a poor ejection fraction in inferior wall myocardial infarction has a high correlation with anterior and/or apical left ventricular dysfunction and that about 40 per cent of such cases can be correctly identified on the basis of VCG criteria for anterior wall myocardial infarction

Marked differences were observed in the severity and extent of coronary obstruction between the abnormal ejection fraction group (A) and normal ejection fraction group (B) Triple vessel disease was twice as common in Group A In contrast single vessel disease was found in only one of 26 patients in Group A (4 7 per cent) whereas in Group B single vessel lesions were observed in nine of 26 patients

It is generally recognized that patients with isolated inferior infarctions have better ventricular function than those with anterior wall pathology However our study strongly suggests that the scalar ECG is not entirely reliable in identifying isolated inferior infarction When vectorcardiography is done in these patients as a supplementary study the diagnosis of occult anterior wall infarction is of great significance Left ventricular hypertrophy dorsal wall infarction and left anterior hemiblock may also be revealed and are clues to more extensive myocardial damage more extensive coronary disease and poor left ventricular emptying Thus vectorcardiography in addition to improving the accuracy of diagnosis of myocardial damage as reported by Burch and associates[17] and Gunnar and associates may also prove valuable in the prediction of ventricular function

Summary

Twenty six patients with ECG evidence of localized inferior myocardial infarction and poor ejection fraction (less than 50 per cent) were compared with 26 patients with similar ECG s but with normal ejection fraction (over 50 per cent) The poor ejection fraction group had significantly more frequent and more severe disease in left anterior descending artery and a higher incidence of triple coronary obstruction than the normal ejection fraction group The poor ejection fraction group had a significantly greater incidence of ventricular asynergy in the anterior and apical segments of left ventricle Vectorcardiography was available in 35 of the 52 patients studied and frequently supplied diagnostic information not available in the scalar ECG s Of 18 patients with scalar ECG patterns of isolated inferior wall infarction and poor ejection fractions vectorcardiography identified five cases with anterior infarction three with left ventricular hypertrophy and one with left anterior hemiblock Vectorcardiography is a valuable supplementary tool in the clinical assessment of patients with apparently isolated inferior infarction When extensive coronary and poor ventricular function exist VCG clues may be expected in about half the patients

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The effect of intravenous digoxin on the occurrence of ventricular tachyarrhythmias in acute myocardial infarction in man

Igor Reicansky
Thor Bjorn Conradson
Stig Holmberg
Lars Rydén
Anders Waldenstrom
Bertil Wennerblom
Goteborg Sweden

There is still considerable debate in the literature as to whether the arrhythmogenic effect of digitalis is increased during acute myocardial infarction (AMI) [1-3] One of the main toxic effects of digitalis is the production of ventricular premature contractions (VPC) Systematic monitoring for arrhythmia detection has been performed in only a few clinical studies dealing with the occurrence of ventricular tachyarrhythmias after digitalization of patients with AMI [4-8] None of these studies was controlled and the concentration of digitalis in serum was not measured and correlated to the occurrence of ventricular tachyarrhythmias

The purpose of this study was to determine the frequency of ventricular tachyarrhythmias in patients with AMI and incipient left ventricular failure before and after the intravenous administration of either normal saline or a therapeutic amount of digoxin given in a double blind fashion

Material and methods

Patients admitted to the coronary care unit (CCU) with a definite AMI (W H O criteria[9]) were considered for the study if they developed signs of incipient left ventricular failure This was defined as the presence of one or more of the following findings (1) a third and/or fourth heart sound (2) persistent post tussive basilar pulmonary rales (3) sinus tachycardia at a rate exceeding 100 per minute for at least 15 minutes Patients who had antiarrhythmic or digitalis therapy prior to admission to the CCU and patients with frank pulmonary edema hypotension (systolic blood pressure < 90 mm Hg) second or third degree atrioventricular (A V) block or sinus bradycardia (rate < 50 per minute) were excluded from the study Patients accepted for the study were allocated to either a digoxin or a control group according to a double blind system of randomization Digoxin (Lanacrist Draco Lund Sweden) 0 01 mg per kilogram of body weight was administered intravenously at a constant rate over a 10 minute period The patients in the control group received a corresponding volume of saline Informed consent was obtained from all patients prior to randomization

Apart from the administration of either digoxin or saline the patients under study were managed and their electrocardiograms (ECG s) monitored according to the normal CCU routine [10] No antiarrhythmic treatment was permitted during the time of study unless ventricular fibrillation ventricular tachycardia (VT = ≥ 3 VPC s in sequence rate > 100 per minute) or ventricular bigeminy persisting for more than 30 second occurred If any of these arrhythmias or the

From the Medical Clinic I, Department of Cardiology, Sahlgrenska Hospital, S-413 4 Goteborg, Sweden

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Reprint requests Dr Anders Waldenstrom Med Clinic I Sahlgrenska Hospital, S-413 4 Goteborg, Sweden

Table I Clinical and laboratory findings in the digoxin and saline groups of patients

	Digoxin (n = 18) No	*Saline (n = 15) No*	*Difference*
Sex			
Male	13	12	NS
Female	5	3	
Age (yr)			
30 39	1	0	
40 49	0	1	
50 59	7	6	
60 69	8	7	
70 79	2	1	
Mean ± SE	60 ± 2	61 ± 2	NS
Site of infarction			
Anterior	6	11	
Posterior	12	4	NS
Delay from start of symptoms to start of infusion (hr)			
Mean ± SE	28 ± 5	32 ± 6	NS
Previous infarction			
0	15	11	
1	2	2	
≥2	1	2	NS
Heart rate at start of therapy			
< 60	0	2	
61 100	16	10	
> 100	2	3	
Mean ± SE	83 ± 4	80 ± 5	NS
Blood pressure at start of therapy (mean ± SE)			
Systolic	129 ± [illegible]	136 ± [illegible]	NS
Diastolic	79 ± 3	86 ± 3	NS
SGOT max (U/L)			
Normal ≤ 17	0	2	
18 100	10	8	
101 200	7	4	NS
> 200	1	1	
Mean ± SE	101 ± 13	93 ± 23	
Potassium (mEq/L) (normal 3 5 5 1)			
Mean ± SE	4 0 ± 0 1	4 0 ± 0 1	NS
Creatinine (mg/100 ml)			
Normal ≤ 1 2	18	14	NS
> 1 2	0	1	
Bilirubin (mg/100 ml)			
Normal ≤ 1 2	17	14	
> 1 2	1	1	NS

above mentioned contraindications for digoxin were discovered on routine monitoring the patient was excluded from the study from that time on

The monitored ECG lead was also continuously recorded using an ink writing recorder (Mingograph 81, Siemens Elema AB Stockholm Sweden) with a paper speed of 10 mm per second On each patient a 1 hour long ECG record preceded the administration of digoxin or saline and was continued for 3 hours following the injection All data concerning the occurrence of ventricular tachyarrhythmias refers to this continuous ECG recording The ECG was interpreted from each individual patient without knowledge of which drug the patient had received All ECG s were analyzed minute by minute A 1 minute interval was accepted as interpretable only if all QRS complexes included could be identified The accepted 1 minute intervals were classified with regard to the presence or absence of the following types of ventricular tachyarrhythmias (1) 1 to 5 VPC s per minute, (2) > 5 VPC s per minute (3) paired VPC s (4) multifocal VPC s (5) *R on T* VPC s, (6) VT defined as above (7) rapid idioventricular rhythm (RIR ≥ 3 VPC s in sequence rate < 100 per minute) The 1 minute intervals were also classified with regard to the presence of A V block of the second or third degree and sinus arrest After classification of each individual 1 minute interval the information obtained was accumulated to the 1 hour period preceding digoxin or saline and the 3 hour period following administration of these drugs The 3 hours following drug administration were also considered as separate successive 1 hour periods The ECG record from each patient was treated individually and the comparisons between the two groups were based on these compiled data Calculations were made of the relative incidence of patients with a specific type of arrhythmia during the defined period of observation as well as the percentage of arrhythmia containing 1 minute intervals observed during this period The method of arrhythmia detection has been described in detail previously [11] The heart rate and brachial artery cuff pressure were measured at regular intervals before and after drug administration A venous blood sample was taken 3 hours after injection of the drug for determination of digoxin in serum The digoxin analyses were run as duplicates (Gamma Coat digoxin Clinical Assays Inc) Intra assay variation was 7 per cent for values ≤ 2 nmol per liter and 10 per cent for values > 2 nmol per liter Blood samples were taken on the day of study for determination of serum levels of GOT, GPT, LDH isoenzymes bilirubin alkaline phosphatase

Table II Physical signs at the start of the investigation

Sign	Digoxin (n = 18) No	Saline (n = 15) No	Difference
S /S	5	5	NS
Basilar râles	3	0	NS
Tachycardia (> 100/min)	1	0	NS
[illegible] /S + basilar rales	[illegible]	6	NS
S /S + tachycardia	2	3	NS
S /S + basilar rales + tachycardia	0	1	NS

S Third heart sound [illegible] fourth heart sound

Table III Over all incidence of patients with the various types of ventricular tachyarrhythmias during the 3 hour period following drug administration

Type of VPC	Digoxin (n = 18)		Saline (n = 15)		Difference
	No	%	No	%	
None	4	22	2	13	NS
1-5/min	10	56	12	80	NS
>5/min	4	22	1	7	NS
Paired	5	28	4	27	NS
Multifocal	2	11	4	27	NS
R on T	0	0	0	0	NS
RIR	[illegible]	[illegible]	1	7	NS
VT	0	[illegible]	1		NS

RIR Rapid [illegible]oventricular rhythm VT ventricular tachycardia

creatinine and potassium The results were compared with Student s t test for independent means χ^2 test and Fisher s exact probability test for the test of independent proportions (large and small samples respectively)

Results

A total of 33 patients were admitted to the study of whom 18 belonged to the digoxin group and 15 to the saline group The patient characteristics are presented in Table I and the physical signs at the start of the investigation are listed in Table II The two groups were clinically comparable in the various aspects which were studied There was no statistical difference between the incidence of the various types of ventricular tachyarrhythmias in the two groups in the 1 hour period preceding drug injection

The administration of digoxin and saline did not change the incidence of ventricular tachyarrhythmias as compared to the 1 hour period before drug injection There was also no statistically significant difference between the two groups as regards the incidence of patients containing the defined types of ventricular tachyarrhythmias when considering the total 3

Table IV Over all incidence of 1 minute intervals containing the various types of ventricular tachyarrhythmias during the 3 hour period following drug administration

Type of VPC	Digoxin n = 3142		Saline n = 2575		Difference
	No	%	No	%	
None	2,885	91 8	2,269	88 1	p < 0 001
1 5/min	246	7 8	297	11 5	p < 0 001
>5/min	11	0 4	10	0 4	NS
Paired	8	0 3	21	0 8	p < 0 01
Multifocal	9	0 3	45	1 8	p < 0 001
R on T	0	0 0	0	0 0	NS
RIR	0	0 0	34	1 3	p < 0 001
VT	0	0 0	2	0 1	NS

Table V Concentration of digoxin in serum at the end of the observation period

Patient No	Concentration (nmol/L)
1	1 2
2	1 6
3	1 7
4	1 5
5	–
6	1 5
	1 9
8	2 8
9	–
10	1.2
11	1 9
12	>5 1
13	1.9
14	1 7
15	3 9
16	1 8
17	1 9
18	–
Mean	1 9
SD	0 7
SE	0 2
No	14

Excluded from the calculation of the mean since the exact level exceed the limit of the method

Table 1 Clinical and laboratory findings in the digoxin and saline groups of patients

	Digoxin (n = 18) No	*Saline (n = 15) No*	*Difference*
Sex			
Male	13	12	NS
Female	5	3	
Age (yr)			
30 39	1	0	
40 49	0	1	
50 59	7	6	
60 69	8	7	
70 79	2	1	
Mean ± SE	60 ± 2	61 ± 2	NS
Site of infarction			
Anterior	6	11	
Posterior	12	4	NS
Delay from start of symptoms to start of infusion (hr)			
Mean ± SE	28 ± [illegible]	32 ± 6	NS
Previous infarction			
0	15	11	
1	2	2	
≥2	1	2	NS
Heart rate at start of therapy			
<60	0	2	
61 100	16	10	
>100	2	3	
Mean ± SE	83 ± 4	80 ± 5	NS
Blood pressure at start of therapy (mean ± SE)			
Systolic	129 ± [illegible]	136 ± 5	NS
Diastolic	79 ± 3	86 ± 3	NS
SGOT max (U/L)			
Normal ≤ 17	0	2	
18 100	10	8	
101 200	7	4	NS
> 200	1	1	
Mean ± SE	101 ± 13	93 ± 23	
Potassium (mEq/L) (normal 3 5 5 1)			
Mean ± SE	4 0 ± 0 1	4 0 ± 0 1	NS
Creatinine (mg/100 ml)			
Normal ≤ 1 2	18	14	NS
>1 2	0	1	
Bilirubin (mg/100 ml)			
Normal ≤ 1 2	17	14	
> 1 2	1	1	NS

above mentioned contraindications for digoxin were discovered on routine monitoring the patient was excluded from the study from that time on

The monitored ECG lead was also continuously recorded using an ink writing recorder (Mingograph 81, Siemens Elema AB, Stockholm Sweden) with a paper speed of 10 mm per second On each patient a 1 hour long ECG record preceded the administration of digoxin or saline and was continued for 3 hours following the injection All data concerning the occurrence of ventricular tachyarrhythmias refers to this continuous ECG recording The ECG was interpreted from each individual patient without knowledge of which drug the patient had received All ECG s were analyzed minute by minute A 1 minute interval was accepted as interpretable only if all QRS complexes included could be identified The accepted 1 minute intervals were classified with regard to the presence or absence of the following types of ventricular tachyarrhythmias (1) 1 to 5 VPC s per minute (2) > 5 VPC s per minute (3) paired VPC s (4) multifocal VPC s (5) R on T VPC s, (6) VT defined as above (7) rapid idioventricular rhythm (RIR ≥ 3 VPC s in sequence rate < 100 per minute) The 1 minute intervals were also classified with regard to the presence of A V block of the second or third degree and sinus arrest After classification of each individual 1 minute interval the information obtained was accumulated to the 1 hour period preceding digoxin or saline and the 3 hour period following administration of these drugs The 3 hours following drug administration were also considered as separate successive 1 hour periods The ECG record from each patient was treated individually and the comparisons between the two groups were based on these compiled data Calculations were made of the relative incidence of patients with a specific type of arrhythmia during the defined period of observation as well as the percentage of arrhythmia containing 1 minute intervals observed during this period The method of arrhythmia detection has been described in detail previously[11] The heart rate and brachial artery cuff pressure were measured at regular intervals before and after drug administration A venous blood sample was taken 3 hours after injection of the drug for determination of digoxin in serum The digoxin analyses were run as duplicates (Gamma Coat digoxin Clinical Assays Inc) Intra assay variation was 7 per cent for values ≤ 2 nmol per liter and 10 per cent for values > 2 nmol per liter Blood samples were taken on the day of study for determination of serum levels of GOT GPT LDH isoenzymes bilirubin alkaline phosphatase

Table II Physical signs at the start of the investigation

Sign	*Digoxin (n = 18)* No	*Saline (n = 15)* No	*Difference*
S/S*	[illegible]	5	NS
Basilar rales	3	[illegible]	NS
Tachycardia (> 100/min)	1	0	NS
S/S + basilar rales	[illegible]	[illegible]	NS
S/S + tachycardia	2	3	NS
S/S + basilar rales + tachycardia	0	1	NS

*Third heart sound S fourth heart sound

Table III Over all incidence of patients with the various types of ventricular tachyarrhythmias during the 3 hour period following drug administration

Type of VPC	*Digoxin (n = 18)* No	%	*Saline (n = 15)* No	%	*Difference*
None	4	[illegible]	2	13	NS
1-5/min	10	56	12	80	NS
>5/min	4	2	1	7	NS
Paired	5	28	4	27	NS
Multifocal	[illegible]	11	4	27	NS
R on T	[illegible]	0	0	0	S
RIR	0	0	1		NS
VT	0	0	1	[illegible]	NS

RIR Rapid idioventricular rhythm VT ventricular tachycardia.

creatinine and potassium The results were compared with Student's t test for independent means, χ^2 test and Fisher's exact probability test for the test of independent proportions (large and small samples respectively)

Results

A total of 33 patients were admitted to the study of whom 18 belonged to the digoxin group and 15 to the saline group The patient characteristics are presented in Table I and the physical signs at the start of the investigation are listed in Table II The two groups were clinically comparable in the various aspects which were studied There was no statistical difference between the incidence of the various types of ventricular tachyarrhythmias in the two groups in the 1 hour period preceding drug injection.

The administration of digoxin and saline did not change the incidence of ventricular tachyarrhythmias as compared to the 1 hour period before drug injection There was also no statistically significant difference between the two groups as regards the incidence of patients containing the defined types of ventricular tachyarrhythmias when considering the total 3

Table IV Over all incidence of 1 minute intervals containing the various types of ventricular tachyarrhythmias during the 3 hour period following drug administration

Type of VPC	*Digoxin n = 3142* No	%	*Saline n = 25[illegible]* No	%	*Difference*
None	2,88[illegible]	91.8	2,[illegible]	88.1	p < 0.001
1-5/min	[illegible]	[illegible]	29[illegible]	11.5	p < 0.001
>5/min	11	0.4	10	0.4	NS
Paired	8	0.3	21	0.8	p < 0.01
Multifocal	[illegible]	0.3	[illegible]	1.8	p < 0.001
R on T	0	0.0	[illegible]	0.0	NS
RIR	0	0.0	34	1.3	p < 0.001
VT	0	0.0	2	0.1	NS

Table V Concentration of digoxin in serum at the end of the observation period

Patient No	*Concentration (nmol/L)*
1	1.2
2	1.6
3	1.[illegible]
4	1.3
5	–
6	1.3
7	1.9
8	2.8
9	–
10	1.2
11	1.9
12	>5.1
13	1.9
14	1.[illegible]
15	3.9
16	1.8
17	1.9
18	–
Mean	1.9
SD	0.7
SE	0.2
No	14

Excluded from the calculation of the mean since the exact level exceeds the limit of the method.

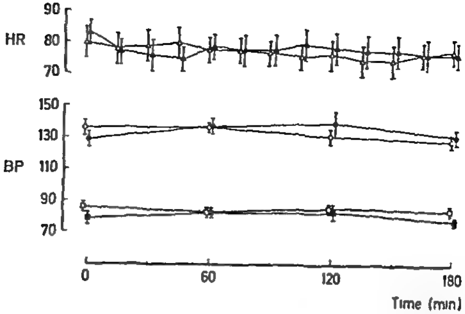

Fig 1 Heart rate and blood pressure before and after the administration of digoxin (filled symbols) and saline (unfilled symbols) respectively The figure presents mean levels ± S E Triangles heart rate circles systolic blood pressure squares diastolic blood pressure

hour period following drug administration (Table III) Considering the 1 minute intervals those without any VPC s were less in the digoxin group (92 per cent) than in the saline group (88 per cent, $p < 0.001$ Table IV) The ECG records during the 3 hours after drug injection were also analyzed as separate consecutive 1 hour periods This was performed in order to detect a possible short lasting arrhythmia provoking effect of digoxin which could be hidden when only considering the total period No differences in arrhythmia content could however be detected during any of the 1 hour periods VT was discovered for short periods on the continuous ECG record in two patients belonging to the digoxin group prior to drug administration and in one patient in the saline group after drug administration These episodes were not detected on routine monitoring therefore, the patients remained in the study during the total time of observation Ventricular fibrillation did not occur in any patient

One patient in the digoxin group had A V block of the second degree, Mobitz type I during three of the 1 minute intervals of the time recorded prior to drug administration This was not detected on routine monitoring and consequently the patient received digoxin The A V block occurred more frequently following digoxin but the patient did not develop complete A V block Sinus arrest was not present more frequently in the digoxin than in the saline group

Digoxin did not cause any significant changes in blood pressure or heart rate (Fig 1)

Serum levels of digoxin at the end of the observation period were available in 15 patients and the results are presented in Table V Even when the cases (Patients No 's 8 12, and 15) with the highest levels of digoxin were considered there was no increased incidence of VPC s observed after digoxin injection

There were no side effects following the administration of digoxin or saline which could be related to the drugs

Discussion

Ever since the experimental works of Bellet and associates[12] and of Travell and associates[13] it has been assumed that AMI enhances the toxicity of digitalis This assumption has been supported by more recent studies on animals[14-16] For instance, Hood and associates[14] reported a 25 per cent reduction in the toxic dose of acetyl strophanthidin following experimental production of AMI in dogs In previous clinical studies however, in patients with AMI there has been no clear cut evidence of an increased occurrence of ventricular tachyarrhythmias following the administration of digitalis[6, 17, 8] The explanation for the contradictory results between the experimental studies on animals and the clinical investigations in man have centered mainly upon the design of the clinical investigations[1, 2, 8] These

criticisms have focused on poor arrhythmia detection systems lack of suitable controls and a lack of a double blind design In patients with AMI the clinical condition and the incidence of ventricular tachyarrhythmias changes from one time to another Accordingly the design of the investigation may have a great influence on the results Further points of criticism are that in many previous investigations the dose of digitalis may have been inadequate and that no correlation was performed between the blood level of digitalis and the occurrence of arrhythmias

In the present double blind study all information concerning arrhythmias was obtained from a continuous ECG record The two groups of patients were comparable in all aspects analyzed Both groups were followed for 1 hour prior to drug administration since it was considered of specific importance to determine the spontaneous occurrence of ventricular tachyarrhythmias This design was also chosen to enable detection of a change in arrhythmia occurrence following administration of the drug The comparison has thus been based on both a patient related and a time related analysis Since some types of VPC s may have a more serious importance than others the analysis of ventricular tachyarrhythmias was performed according to the criteria suggested by Lown and associates as indications for treatment of ventricular arrhythmias in AMI The results show that digoxin did not increase the occurrence of any type of ventricular tachyarrhythmia On the contrary there were fewer 1 minute intervals with any type of VPC s in the digoxin than in the saline group as was the case with some of the different types of VPC s (Table IV) Although statistically significant these findings should not be used as *evidence of a proved arrhythmia* protecting property of digoxin The differences were not present during the separate 1 hour periods following drug administration and were not confirmed by a decrease in the number of patients with ventricular tachyarrhythmias

The lack of agreement between the present results and experience gained from animal studies has no obvious *explanation* First it must be considered whether the *dose* of digoxin was large enough to give adequate serum levels *In all the* patients the serum concentration of digoxin *was* well above what is considered *the minimum* therapeutic level and in three *patients* it approached or reached the toxic range [5] *Recent* findings in animals suggest that toxic effects of digitalis may occur at lower serum concentrations in connection with AMI than otherwise [13, 25] This alteration of sensitivity [21, 2] has been attributed to uneven distribution of digoxin in the infarcted area of the myocardium These findings are not however confirmed by the present study where an increased occurrence of ventricular tachyarrhythmias was not observed in patients with the highest digoxin levels or in patients who presented evidence of an extensive myocardial infarction as judged from ECG and enzyme elevations.

It has been reported that digitalis may decrease the number of VPC s occurring in patients with cardiac insufficiency [3] *Thus a possible* explanation for the lack of agreement between the experimental findings in animals and the *present* clinical study may be that digitalis *produced* beneficial hemodynamic effects in *the patients* with incipient left ventricular *failure which counteracted* a possible arrhythmia provoking mechanism Although such an effect cannot be ruled out it is unlikely to be of a *great importance* as no statistically significant changes were observed in the blood *pressure* or heart rate following the administration of *digoxin* Furthermore previous findings *in patients in* a similar hemodynamic *state showed* limited hemodynamic effects of digoxin [4, 3, 10] It has been suggested that the sensitivity to digitalis during AMI is mainly *related to* accompanying complications such as *electrolyte* imbalance acidosis hypoxia and increased sympathetic activity rather than to the *presence* of myocardial cell damage per se [3] The *results* of the present study are consistent with this statement A further and probably important *explanation* of the above mentioned lack of agreement is the limited relevance of conclusions *drawn* from experimental observations in animals when comparing human beings in a diseased *state*

The conclusion of this study is *that* patients with AMI complicated by *incipient left* ventricular failure do not show an increased sensitivity to a normal *therapeutic* amounts of digoxin as measured by the *occurrence* of ventricular tachyarrhythmias

Summary

Patients with *acute* myocardial infarction were allocated to two groups according to a double

blind system of randomization The patients (n = 18) in one of the groups received digoxin intravenously as an injection of 0 01 mg per kilogram of body weight during 10 minutes The patients in the other group (n = 15) received saline and served as controls A continuous ECG record was obtained from each patient during 1 hour preceding the administration of digoxin or saline and was continued for 3 hours following the injection No antiarrhythmic treatment was given during the time of the study Based on the continuous ECG, calculations were made of the relative incidence of patients with different types of ventricular tachyarrhythmias during the period of observation as well as the percentage of arrhythmia containing 1 minute intervals observed during this period

There was no statistical difference between the incidence of ventricular tachyarrhythmias in the two groups in the 1 hour period preceding drug injection The administration of digoxin and saline did not change the incidence of ventricular tachyarrhythmias and there was also no statistically significant difference between the two groups as regards the incidence of patients showing different types of ventricular tachyarrhythmias during the 3 hour period following drug administration Considering the 1 minute intervals those without any ventricular premature contractions were less in the digoxin group (92 per cent) than in the saline group (88 per cent $p < 0.001$)

Serum levels of digoxin at the end of the observation period were well above what is considered the minimum therapeutic level and in three patients the level approached or reached the toxic range In these three patients there was still no increased incidence of ventricular tachyarrhythmias It is concluded that patients with acute myocardial infarction complicated by incipient left ventricular failure do not show an increased sensitivity to an ordinary dose of digoxin as measured by the occurrence of ventricular tachyarrhythmia

The digoxin analyses were performed by Assistant Professor Goran Lindstedt at the Laboratory of Clinical Chemistry Sahlgren s Hospital Göteborg, Sweden

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The effects of smoking on myocardial conduction in the human heart

Soad Bekheit, M D
Evan Fletcher, M D
Houston, Texas

Sufficient quantities of nicotine are absorbed from the mucous membrane of the mouth and respiratory tract during cigarette smoking to induce acute effects on the cardiovascular system[1] Hitherto most observations have been made on central and peripheral hemodynamic responses to smoking[2,3] Less attention has been paid to electrophysiological effects, although minor T wave changes in scalar tracings ascribed to the associated tachycardia have been noted[4] In this paper the effect of cigarette smoking on conduction velocity in the specialized tissues of the human heart is described Measurements of the increments of atrioventricular (A V) conduction were made from His bundle electrograms and scalar leads A brief resume of the quality of tobacco smoke and the pharmacological action of nicotine is outlined before descriptions of methods employed in our experiments and interpretation of the results

Tobacco smoke is an aerosol to which nicotine is attached in its active levorotatory form The average commercial cigarette contains about 10 mg of nicotine of which 3 mg is taken into the mouth in the mainstream smoke[1] The remainder is dissipated in the sidestream smoke and the butt or lost by pyrolysis[1] During smoking the aerosol is administered by repetitive booster doses or puffs Each cigarette contains 10 to 12 puffs In our experiments absorption of nicotine was proved by urinary nicotine levels Although the amount of nicotine absorbed must be minute it

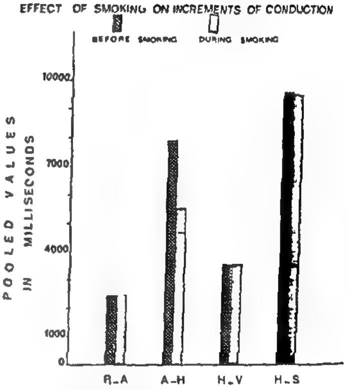

Fig 1 A V nodal conduction time (AH) is shortened during smoking Atrial conduction (P A) His Purkinje-system conduction (HV) and intraventricular conduction (HS) are not significantly altered

nevertheless was sufficient to affect A V conduction as will be evident from the results The subjects chosen for this study were instructed to smoke their accustomed commercial brand of Virginia tobacco cigarette according to their own particular habit In spite of the artificial environment of the Cardiac Catheterization Laboratory, all subjects succeeded in doing do We believe therefore that the conditions of our experiments reflect the changes in myocardial conduction which occur during ordinary social smoking[5] The other known chemical constituents of tobacco smoke such as nicotimine nornicotine

From the Division of Cardiology Program in Internal Medicine University of Texas Health Science Center at Houston Medical School Houston Texas

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Reprint requests Evan Fletcher M D Director Division of Cardiology The University of Texas Health Science Center at Houston 6400 W Cullen St Houston Texas 77025

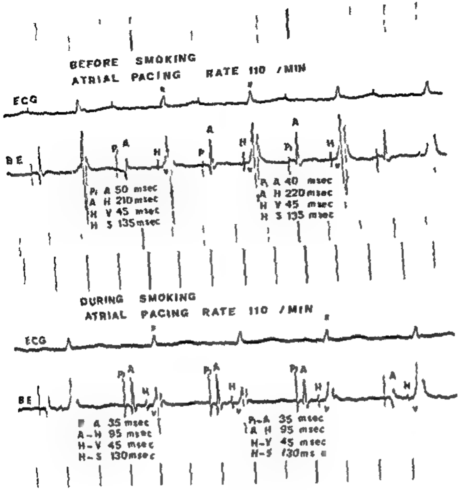

Fig 2 Effect of smoking on A V nodal conduction Note marked shortening of AH interval from 210 to 95 msec during smoking

cotinine and anabasine form only 2 to 5 per cent of the total alkaloids[11] Their low concentration and weak pharmacological action are overshadowed by those of nicotine and may be discounted as far as the acute effects of smoking on the heart are concerned Carbon monoxide and cyanide are also present in tobacco smoke and may produce chronic effects on the nervous system[12] but they are unlikely to affect the results of our experiments The effects of smoking on myocardial conduction therefore are ascribed to the pharmacological action of nicotine alone

Material and Methods

Twenty-eight subjects were studied All had been habitual smokers for more than 10 years Their consent was obtained after the methods of recording and the purpose of the experiment were explained Their routine surface electrocardiograms (ECG) showed (1) sinoventricular conduction via the normal pathways (16 subjects) (2) Wolff Parkinson White (WPW) syndrome (two subjects), (3) Wenckebach block (two subjects) and (4) atrial fibrillation (eight subjects) Smoking was prohibited for 12 hours before each study Ammonium chloride (0 6 Gm) was given orally three times daily for 2 days before each experiment to assure an acid urine which facilitates the excretion of nicotine[1] The subjects were asked to empty their bladders and then drink 500 ml of fluid before entering the catheterization laboratory A specimen of urine was collected immediately preceding cardiac catheterization and retained as a baseline specimen for nicotine content Urinary specimens were collected at hourly intervals for 4 hours after completion of smoking one cigarette The volume and pH of each specimen of urine were measured Nicotine

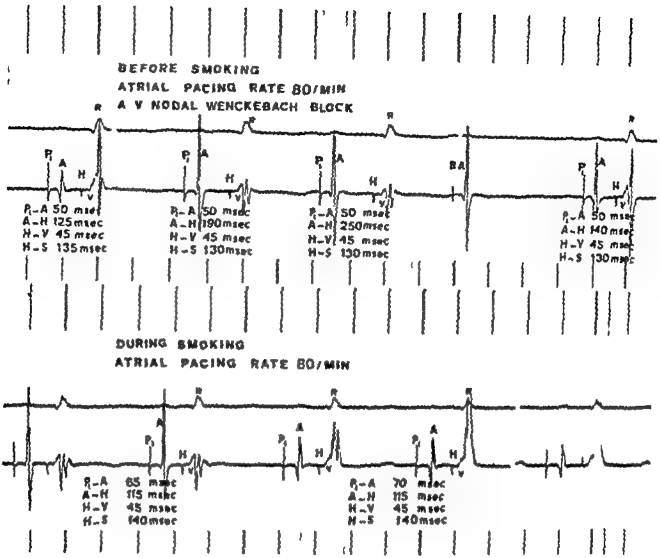

Fig 3 Effects of smoking on Wenckebach block induced by atrial pacing. During smoking the AH interval is shorter and blocked beats are abolished.

estimation was determined by solvent partition with gas liquid chromatography and creatinine levels with the Jaffe reaction.[16]

Measurements of increments of myocardial conduction were made from His bundle electrograms recorded simultaneously with a scalar lead[17] except in eight subjects with atrial fibrillation. The A V conducting pathways were stressed by atrial pacing in the 16 subjects with sinoventricular conduction via the normal pathways and in the two subjects with WPW syndrome. Atrial pacing was carried out at sequential increments of 10 beats between 70 and 150 beats per minute.[18, 19] The tracings obtained are referred to as the "control tracings." Atrial pacing was not carried out in the two subjects who had spontaneous Wenckebach block. A cigarette was lighted and placed in the subject's free left hand, and he was instructed to smoke in his usual manner. Immediately after the first puff sequential atrial pacing at identical rates to the control tracings was repeated. These tracings are referred to as "nicotine tracings." The duration of smoking a single cigarette for the group as a whole was 10 to 12 minutes. The nicotine tracings were completed during smoking of one cigarette. It may be noted that the lower paced rates of the nicotine tracing reflect changes in conduction during the first one to five puffs (the half smoke) and the higher paced rates the cumulative effects of the additional puffs (total of 10 to 12 puffs per cigarette). The following measurements were made from His bundle recordings in the control and nicotine tracings: intra atrial conduction time (P_1A), A V nodal conduction time (AH), His Purkinje system conduction time (HV), and total intraventricular conduction time (HS). In subjects with WPW syndrome AQ interval was measured from the commencement of the A wave of His electrogram to the onset of Q wave of the scalar tracing.

Table I Effects of smoking cigarettes on A V nodal conduction

Subject No	*Rate of atrial pacing per minute* 80	90	100	110	120	130	140	150	Pooled AH†
1 C/N		80/70	95/75	100/70	105/80				380/295
2 C/N		120/90	140/100	210/95	230/100	240/120	W/125‡	W/175	940/805
3 C/N		80/80	90/80	120/80	130/80	140/80	200/120	200/120	960/640
4 C/N		110/105	115/70	120/80	130/90				475/345
5 C/N		70/70	75/75	80/85	95/85	110/90	115/100	120/110	665/615
6 C/N	100/85	105/90	110/100	135/120	165/130	W/1[illegible]0	W/W		615/525
7 C/N	W/115	W/140	W/165	W/W					
8 C/N		115/100	125/100	135/110	140/130	155/135	W/W		670/575
9 C/N		70/55	75/45	80/65	85/70	100/90	110/95	W/105	520/420
10 C/N				75/55	W/60	W/65	W/70		75/55
11 C/N		110/100	120/105	130/110	140/120	W/135	W/170		500/435
12 C/N			95/85	110/90	115/90	W/95	W/90	W/95	320/265
13 C/N		70/50	70/60	80/65	85/65	90/70	105/75	110/90	610/475
14 C/N		85/65	100/85	115/100	120/105				420/355
15 C/N			95/65	100/70	115/75	120/85	125/90	135/105	690/490
16 C/N					85/60	90/65	100/65	110/75	385/265
t test		P<0.025	P<0.0005	P<0.005	P<0.0025	P<0.0025	P<0.0025	P<0.01	P<0.0005

C = control tracing N = nicotine tracing
†Pooled AH = sum of AH intervals for each subject
‡W = Wenckebach block

Table II Effects of cigarette smoking on conduction pathways in WPW syndrome

	Atrial paced rates/min 80		90		100		110		120		130	
Increments of conduction	AQ C/N	AH C/N	AQ C/N	AH C/N	AQ C/N	AH C/N	AQ C/N	AH C/N	AQ C/N	AH C/N	AQ C/N	AH C/N
Case No 1	75/75	105/85	75/75	125/95	75/75	150/130	75/75	160/135	75/75	W/140	75/75	W/160
Case No 2	—	—	55/55	70/65	55/55	80/70	55/55	90/75	55/55	120/100	55/55	135/105

AQ = anomalous pathway conduction time (msec) AH = AV nodal conduction time (msec)

projected onto the His bundle baseline which measures conduction time through the anomalous pathways All measurements were made in milliseconds The pacing and recording electrodes were maintained in the same position during all recordings

In the eight subjects with atrial fibrillation, the same technique for smoking was employed and changes in A V *conduction time* were deduced from changes in the ventricular cycle length measured from the scalar tracings The average ventricular rate was calculated with the subjects recumbent over a period of 1 hour for control tracings and during smoking over a period of 10 to 12 minutes for the nicotine tracings All eight subjects were on maintenance digitalis therapy

Results

Effect of smoking on A V conduction Fig 1 illustrates the effect of smoking one cigarette on the increments of conduction for the group of 16 subjects with A V conduction via the normal pathways during sequential atrial *pacing* A V nodal conduction time (AH interval) was significantly shortened during smoking In contrast intra atrial conduction (P-A) His Purkinje-system conduction (HV), and total intraventricular conduction (HS) were *not* altered by smoking Fig 2 illustrates these *effects* in one of the subjects The absolute values of A V nodal conduction time at *paced* rates between 80 and 150 beats per minute in the control and nicotine tracings in 16 subjects with conduction via the

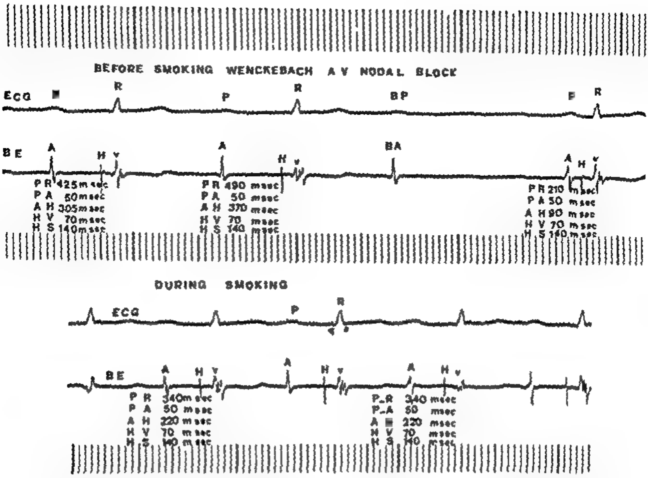

Fig 4 Abolition of spontaneous Wenckebach block during smoking B4 = blocked A wave During smoking AH interval is shortened and no beats are blocked

normal pathways are shown in Table I For purposes of comparison the AH intervals at each paced rate for each subject were summated and expressed as a pooled number The difference between the pooled number of the 'control' (C) and 'nicotine' (N) tracings for the 16 subjects was highly significant (P = < 0 0005) Also, comparison of the AH intervals in the 'control and nicotine tracings showed increased velocity of A V nodal conduction at the lower paced rates, i e, during the half smoke' Thus at paced rates of 100 beats per minute, the shortening of the AH interval for the whole group during smoking was highly significant (P = < 0 005) (Table I) These results confirm that after a few puffs of one cigarette, the velocity of A V nodal conduction is increased under the stress of atrial pacing

Abolition of blocked beats The progressive prolongation of A V nodal conduction time (AH interval) was terminated by *blocked beats in* eight of the 16 subjects studied between paced rates of 80 and 130 beats per minute (Table I Cases 2 and 6 to 12) Blocked beats were abolished in the nicotine tracings in all instances except in *one subject (Table I Case 8) Fig 3 illustrates this* effect in one subject (Table I Case 7) In the two subjects with spontaneous Wenckebach block smoking also abolished the blocked beats (*Fig* 4)

Effect of smoking on WPW syndrome Table II shows measurements of conduction in the normal and anomalous pathways during atrial pacing at sequential rates between 80 and 130 beats per minute in two subjects with WPW syndrome In each subject the AQ interval which represents conduction through the anomalous pathway was identical at this range of paced rates in the control' tracings and it was not altered at any paced rate in the 'nicotine' tracings Smoking therefore had no effect on the velocity of conduction in the fibers of the anomalous pathways In contrast the AH *intervals which represent* conduction via the A V nodal pathways were *progressively prolonged at increasing paced rates* in the control and nicotine tracings but they were shorter in the nicotine tracings (Fig 5) In one *subject (Fig 6)* it was noted that at faster paced rates the H deflection appeared to move

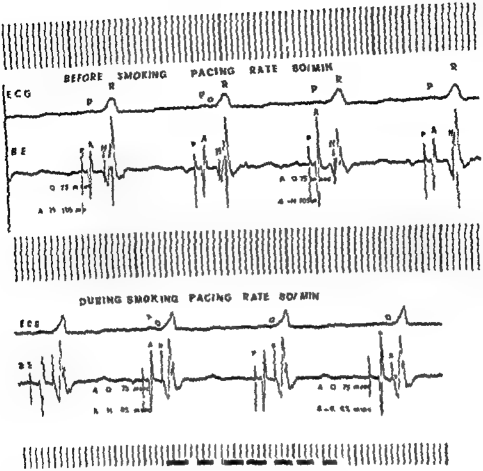

Fig. 6. Effects of smoking on Wolff-Parkinson-White syndrome during atrial pacing (Table 2, Case 1). Anomalous conduction velocity (AQ) is not altered. *Atrioventricular nodal conduction is shortened from* 105 msecs. to 65 msecs. Note change in QRS configuration during smoking.

within the ventricular complex and in some complexes the ventricles seemed to be activated by the anomalous pathway alone, i.e., the impulse was completely blocked in the A-V node. However, during smoking the conduction velocity was increased in the A-V node as evidenced by the shorter AH intervals so that the impulse could reach the ventricles by both pathways.

Effects of smoking on atrial fibrillation. The ventricular rate was promptly increased in atrial fibrillation after one to three puffs of a cigarette and maintained through the smoking period (Fig. 7). For the group as a whole the average increase in rate was 22.4 *per cent.*

Urinary nicotine levels. During *smoking* nicotine absorption was confirmed by increased urinary nicotine excretion. *The maximum* values were reached 1 hour after completion of smoking. The summation of nicotine values in all specimens of urine collected in the 4 hour period *after smoking showed* a marked rise (range 716 to 1,967 µg per gram of creatinine), compared with *the control* values (range 99 to 375 µg per gram of creatinine).

Discussion

Previous studies have confirmed that smoking causes an increase in the sinus rate.[4, 5] The present investigation showed that smoking alters myocardial conduction and defines *more precisely* its effect on the different sites of the conducting pathways. The results revealed that smoking a single cigarette increased the velocity of conduction in the *A-V node* and shortened its effective refractory period. As the observations were made during *atrial* pacing, the changes in A-V nodal conduction were specific and not dependent on the *effects of* nicotine on the sinus rate. Under the conditions of the experiment conduction was not altered in the Purkinje fibers

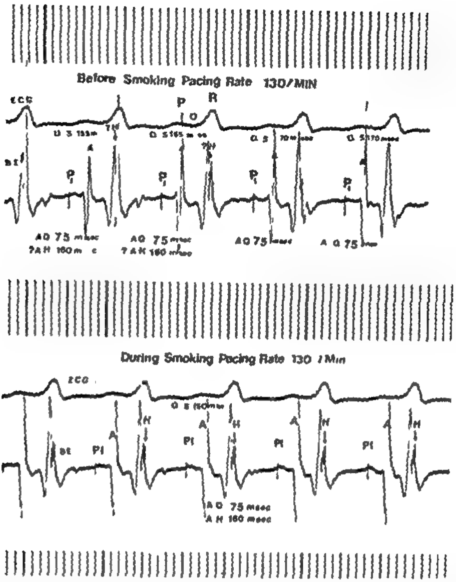

Fig 6 Effects of smoking in WPW syndrome Anomalous conduction velocity is not altered (AQ = 75 msec) H waves cannot be identified with certainty Progressive prolongation of QS intervals from 155 to 170 msec strongly suggest increasing delay and block in the A V node During smoking the QS interval is fixed at 150 msec which may indicate preservation of conduction in the dual pathway

of the ventricles These specific effects of smoking on conduction in the A V node are explained by the adrenergic stimulant effect of nicotine This stimulant effect was strong enough to abolish Wenckebach block induced by artificial atrial pacing A similar action may explain the abolition of spontaneous Wenckebach block in the two subjects described above It is of interest that the AQ interval in the subjects with the WPW syndrome not only remained constant at the different paced rates applied in the experiment but also was not altered by smoking In this respect therefore, the anomalous conduction fibers resemble the Purkinje fibers in the ventricles As A V nodal conduction velocity is increased by smoking the balance between the two pathways which determines the mechanism of ventricular depolarization is altered For example, when the ventricles are entirely activated by the anomalous pathway, smoking results in ventricular activation by the dual pathways as the effective refractory period of the A V node is decreased The increased velocity of A V nodal conduction more effectively competes with anomalous pathways during smoking Since re entry or circuit tachycardias in patients with WPW syndrome depends upon dual pathways with different conduction velocity, smoking may potentially establish or block a re entry mechanism as it selectively alters conduction in one pathway Further study of the effects of smoking on re entry tachycardias in the WPW syndrome may help to determine the importance of this hypothesis

The increased ventricular rate in atrial fibrillation during smoking is explained by the increased velocity of conduction and shortening of the refractory period of the A V node by nicotine stimulation As the effect is immediate and sustained it has considerable clinical significance especially in such conditions as mitral stenosis as the period of ventricular filling is shortened Also these observations confirm that the adrenergic effect of nicotine was strong enough to antagonize the cholinergic effect of digoxin on A V nodal conduction velocity

The quantitative response of A V nodal conduction to smoking is of interest Although all the subjects were excreting small amounts of nicotine in the control specimens of urine the inhalation of one or two puffs of smoke caused an immediate acceleration of A V nodal conduction velocity Moreover the degree of accelerated conduction was maximal during the half smoke Since each puff of smoke contains about 0 25 mg of nicotine the powerful pharmacological action of the alkaloid on conduction is demonstrated Comroe has shown that small amounts of nicotine act on chemoreceptors in the aortic and carotid bodies to produce adrenergic stimulation via efferent pathways independent of any direct action on automatic ganglia Such a mechanism may explain the immediate stimulation of the A V nodal fibers by minute amounts of nicotine absorbed from the first few puffs of a cigarette Subsequent repetitive booster doses of nicotine during the whole smoke may maintain increased A V nodal conduction velocity by direct action on autonomic ganglia and by liberation of catecholamines from the adrenal medulla and from the chromaffin cells in the myocardium Although the amount of nicotine excreted varied widely due to such factors as degrees of inhalation and degradation by the liver the effect on conduction seems to reflect a maximum response to minute amounts of nicotine Finally habitual smokers do not appear to develop tolerance to this particular pharmacological action of nicotine

Summary

Inhalation of a few puffs on a cigarette increases the velocity of conduction and shortens the effective refractory period of the A V node These effects are attributed to adrenergic stimulation produced by minute amounts of nicotine absorbed Wenckebach block is abolished whether induced by atrial pacing or occurring spontaneously Conduction velocity in the His Purkinje system and in the anomalous pathways in the WPW syndrome were not affected Smoking increases the ventricular rate in atrial fibrillation and antagonizes the cholinergic effects of digitalis

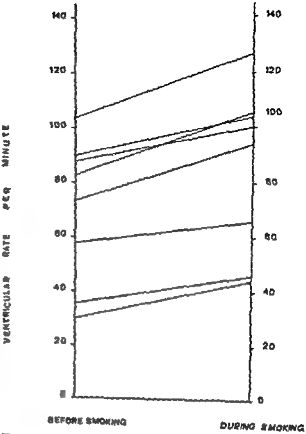

Fig 7 Effect of smoking on ventricular rate in atrial fibrillation.

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Comparison of selective left ventriculograms with levophase ("forward") ventriculograms in patients with coronary artery disease

Jack Ferlinz, M.D.
Michael V. Herman, M.D.*
Peter F. Cohn, M.D.
Richard Gorlin, M.D.*
Boston, Mass.

Left ventricular (LV) cineangiograms are essential for a complete evaluation of patients with coronary artery disease. LV ejection fraction (EF) determined from these studies is used routinely as an index of LV contractility. Further, the adequacy of the LV EF is frequently employed as a criterion for the selection or rejection of patients for coronary artery bypass surgery.

LV EF is usually determined from cineangiograms of *selective* injection of contrast medium into the LV cavity. Many investigators in the past[1,2] have injected contrast medium into the right ventricle or the pulmonary artery and filmed the LV as the dye passed through, obtaining levophase ("forward") left ventriculograms. A few investigators continue to employ this approach in preference to selective LV injection.

The purpose of this study was to evaluate the quality of levophase ventriculograms as compared to selective left ventriculograms and to determine if selective ventriculograms and levophase ventriculograms can be used interchangeably.

Materials and methods

Ten patients with suspected coronary artery disease (CAD) were selected for this study. Seven of them were male and three were female; their mean age was 44 years. All gave informed consent and underwent diagnostic catheterization including complete left and right heart hemodynamic evaluation, cardiac output determination with the green dye indicator dilution technique, selective and levophase left ventriculography, and coronary arteriography. All patients were in normal sinus rhythm. None had systemic hypertension, overt congestive heart failure, or significant valvular or congenital lesions.

Selective left ventriculograms were obtained with a No. 8 Cordis Pigtail catheter that was positioned in the left ventricle. Then 45 to 50 ml of 76 per cent meglumine sodium diatrizoate (Renografin 76) were injected with a power injector over a 3 to 4 second interval. Levophase injection was performed at least 60 minutes after the selective injection and at least 30 minutes after coronary arteriography and only if heart rate, cardiac output, and right- and left-sided pressures remained essentially unchanged in comparison with the values that were recorded just prior to the selective LV injection. For levophase ventriculograms a No. 8 Eppendorf catheter was positioned in the outflow tract of the right ventricle and 55 to 65 ml of Renografin 76 were injected over a 3 to 4 second interval. The additional amount of contrast medium was

From the Cardiovascular Division, Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Mass.

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Reprint requests: Dr. Jack Ferlinz, Chief, Cardiac Catheterization Laboratory, Veterans Administration Hospital, 5901 E. Seventh St., Long Beach, Calif. 90801.

*Dr. Herman is presently Chief, Division of Cardiology and Dr. Gorlin is Professor and Chairman, Department of Medicine at the Mount Sinai School of Medicine, New York, N.Y.

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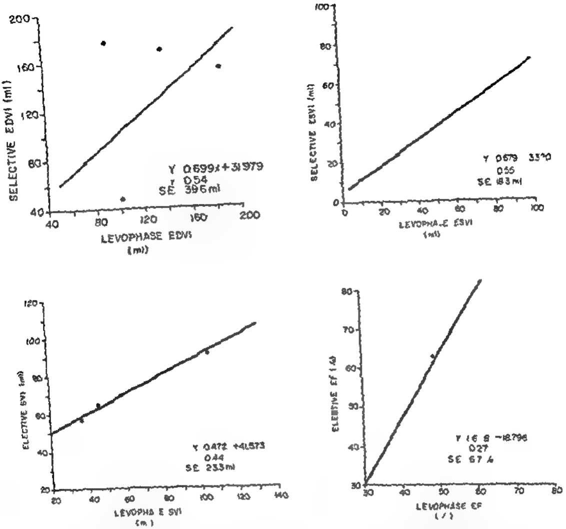


Fig 3 Correlation between selective and levophase values for (upper left) end-diastolic volume index (EDVI) (upper right) end systolic volume index (ESVI) (lower left) stroke volume index (SVI) and (lower right) ejection fraction (EF) Considerable scatter and poor correlation is present in all four panels Nine out of 10 patients have a lower ejection fraction with levophase methodology

EF s have been strongly correlated with prognosis for survival prior to open heart surgery [12,1] Single plane cine ventriculography is often sufficient for proper evaluation of LV motion and accurate calculation of LV EF [1] With extensive CAD however asynergy often supervenes [4,1] When evaluating LV asynergy biplane LV cineangiography not only delineates septal and posterolateral borders of the LV chamber (that are not visualized on a standard 30 degree RAO ventriculogram) but it also enables a more accurate assessment of the LV EF Biplane LV cine ventriculography was therefore used in our study as we were dealing with a patient population that was predisposed to have a significant LV dysfunction

In order to eliminate the pharmacological effects of the contrast medium on myocardial contractility at least 60 minutes were allowed to elapse before a *repeat* ventriculogram was performed This time period is sufficient to dissipate the myocardial depressant effect of the contrast medium [8] Further at least 30 minutes were allowed to elapse after the coronary cineangiography in order to avoid the possible effects of transient reactive hyperemia on myocardial contractility [13,1]

It is by now well established that the error of

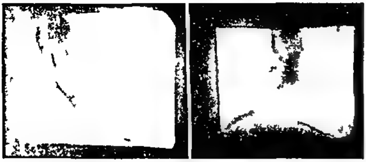


Fig 1 Selective left ventriculogram in 30 degree right anterior oblique (left panel) and 60 degree left anterior oblique (right panel) projections in end-diastole

Fig 2 Levophase (forward) ventriculogram in 30 degree right anterior oblique (left panel) and 60 degree left anterior oblique (right panel) projections of the same patient in end diastole

Table I Comparison of selective vs levophase ventriculograms

	EDVI (ml)	*ESVI (ml)*	*SVI (ml)*	*EF (%)*
Selective injection	102 ± 47	35 ± 22	66 ± 26	67 ± 7
Levophase	100 ± 37	47 ± 18	53 ± 25	52 ± 12
Correlation coefficient (r)	0.54	0.55	0.44	0.27
Statistical significance (p)	NSD*	NSD	< 0.02	< 0.01

*NSD no significant difference

injected for levophase studies in an effort to obtain better cineangiographic resolution

Biplane cineangiograms in 30 degree right anterior oblique (RAO) and 60 degree left anterior oblique (LAO) positions were recorded at 100 frames per second on 16 mm Kodak Plus X film with Siemens 9 inch image intensifier x ray systems Only the first five beats after complete opacification were analyzed by two independent observers If premature ventricular contraction (PVC) was encountered, at least two successive normal sinus beats (following a PVC) had to occur before a frame was selected for analysis

A typical selective ventriculogram frame is presented in Fig 1 and a levophase ventriculogram frame from the same patient in Fig 2 A fourth beat after the complete opacification is presented in each case all occurring in end diastole

A modification[4] of the area length method of Dodge[10] was used in the analysis of all left ventricular volumes End diastolic volume index (EDVI), end systolic volume index (ESVI) stroke volume index (SVI) and ejection fraction (EF = SVI/EDVI) were calculated for each patient

Coronary artery anatomy was evaluated in all 10 patients studied Significant coronary artery disease was considered to be present when the lesion exceeded 75 per cent of the coronary artery lumen

Results

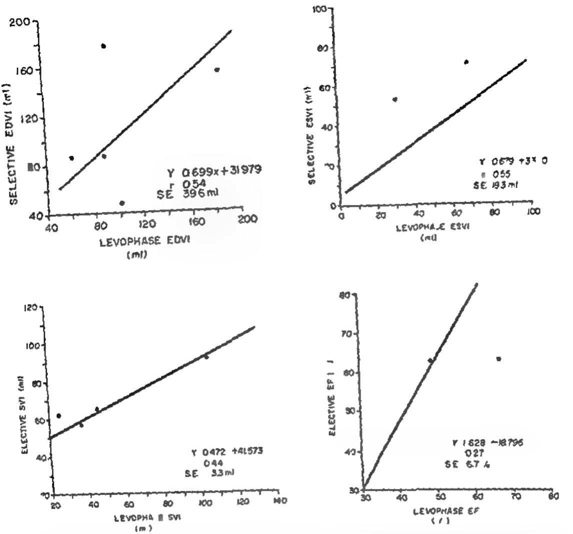
Of the 10 patients studied, five had 75 per cent or greater obstruction of at least one coronary artery, three had documented old anteroseptal infarction and two had old inferior myocardial infarction Variable degrees of LV asynergy were present in all patients with previous myocardial infarction Five patients had mild diffuse CAD, with none of the lesions exceeding 50 per cent of the coronary arterial lumen

The general cine resolution was not as precise in the levophase as in the selective ventriculograms despite the added amount of contrast medium used Further exact tracing of the base of the levophase ventriculograms was often not possible because of the superimposed left atrial opacification, particularly in the 60 degree LAO view (see Figs 1 and 2)

The complete results are given in Table I and respective regression equations are illustrated in Fig 3 Selective ventriculogram SVI and EF were significantly higher ($p < 0.02$ and 0.01 respectively) than their levophase counterparts Further correlation coefficients for the two methods were very low attaining a value of only 0.27 when selective and levophase EF were compared Levophase EF was 52 ± 12 per cent representing an average difference of 15 per cent in comparison to the selective EF (67 ± 7 per cent)

Discussion

LV EF is one of the most accepted standards of LV performance[11] The specific values for LV



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In order to eliminate the pharmacological effects of the contrast medium on myocardial contractility at least 60 minutes were allowed to elapse before a repeat ventriculogram was performed This time period is sufficient to dissipate the myocardial depressant effect of the contrast medium [3] Further at least 30 minutes were allowed to elapse after the coronary cineangiography in order to avoid the possible effects of transient reactive hyperemia on myocardial contractility [8, 11]

It is by now well established that the error of

the selective LV angiographic method (with the appropriate regression equation) falls within the ±20 per cent of the true LV volumes in angiographic LV volume analysis. Concern has been expressed that injections directly into the LV (1) will unnaturally distend the chamber and therefore increase the SV by the Frank-Starling mechanism, (2) may alter myocardial contractility because radiopaque dye is pharmacologically active, and (3) will cause so many PVC's as to make a valid analysis impossible. Various investigators[1-10] have shown that direct injection into the LV chamber changes the LV parameters quite insignificantly. Further, it has been demonstrated that selective left ventriculography can be performed before the significant changes in LV function take place.[15, 23] Finally, careful positioning of the LV catheter greatly minimizes the incidence of PVC's.

Levophase cineangiograms were routinely employed in the early days of LV volume analysis.[5, 7] It was appreciated even then that in subjects with heart enlargement it was often not possible to obtain a satisfactory degree of left ventricular opacification with right heart injection.[6] More recently Cohn and associates[8] have observed in a small number of patients that the cine resolution of the levophase injection was much less precise than of the selective LV injection. Sandler[23] recommended selective LV injection for maximal definition of image margins. Hood and Rackley[27] maintained that only in an occasional adult and only when the patient has a small heart and a thin chest, will a right-sided injection be satisfactory for outlining the left ventricle. In agreement with these findings only Graham and associates[24] were able to show a good correlation between the LV volumes derived from the levophase and the selective LV cineangiograms. All of their patients, however, were children, who (by definition) satisfy the criteria outlined by Hood and Rackley.[27] The comparable anatomy is of course only very rarely present in the adult population with CAD.

Inferior cine resolution with a right-sided injection is due to the substantial dilution of the contrast dye by the time it arrives to the LV. This dilution can not be completely overcome even with the maximal amount of contrast medium that can be safely injected into the right ventricle or pulmonary artery. When the LV chamber is dilated as a consequence of disease, the cine resolution becomes even poorer. Thus, patients who are in the greatest need of precise LV evaluation because of seriously compromised cardiac status have generally the poorest quality ventriculograms and LV volumes and EF's derived from them are often only imprecise estimates.

Aside from the inferior cine resolution of levophase angiograms, the precise tracing of the end-systolic and end-diastolic levophase outlines is further hampered by the superimposition of the opacified left atrium. This is particularly true in the LAO view, where left atrium often completely obscures the base of the LV (see Fig. 2).

Some investigators who employ levophase ventriculograms for their LV analysis have had a great success in operating on patients with extremely low EF's as determined by this method.[5, 8, 15] Their results generally differ with the experience of the majority of medical centers who report prohibitive surgical morbidity and mortality rates if LV EF is 25 per cent or less[11, 13] when selective injection is utilized.

Selective and levophase LV EF's cannot be used interchangeably because levophase ventriculograms significantly underestimate (in our series in nine out of 10 patients) the LV EF when compared to selective LV angiograms. It is therefore quite possible that the interinstitutional differences in surgical survival of patients with very low EF's can be traced directly to differences in methodology used to obtain LV cineangiograms. These differences must be appreciated before a decision for surgical intervention is accepted or rejected on the basis of the angiographic data.

Summary

In order to compare levophase ("forward") ventriculograms to standard (selective) LV cineangiography, 10 patients with coronary artery disease were studied by (1) selective injection of contrast medium into the LV cavity followed by (2) injection into the right ventricle and filming the levophase. Biplane cineangiograms were used to calculate the end-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume index (SVI), and ejection fraction (EF). Values for the two respective techniques were then compared.

Not only were correlation coefficients for the two methods low, but there was also a statisti

cally significant difference between the two SVI (66 ± 26 ml for selective and 53 ± 25 ml for levophase injection $p < 0.02$) and the two EF (67 ± 7 per cent for selective and 52 ± 12 per cent for levophase injection $p < 0.01$) Levophase cineangiograms therefore significantly underestimate the LV ejection fraction when compared to standard (selective) LV cineangiography These differences must be considered when evaluating greatly divergent interinstitutional survival rates for patients with low EF who undergo coronary artery bypass surgery and when selecting candidates for bypass surgery on the basis of the angiographic data

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Relationship between duration of systolic upstroke of apexcardiogram and internal indexes of myocardial function in man

Jan Manolas, M.D.
Pierre Wirz, M.D.
Wilhelm Rutishauser, M.D.
Zurich, Switzerland

The left apexcardiogram (ACG), a low frequency record of precordial displacement at the point of maximal heart beat caused by the motion of the left ventricular wall in relation to the chest, has been used primarily for qualitative descriptions of various cardiac diseases[1, 2] and as a guide in interpretation of the phonocardiogram.[3, 4] Recently it has been demonstrated that the ACG reflects left ventricular events in a qualitative[5-8] and possibly also in a quantitative fashion.[9-17] This study was undertaken to evaluate the usefulness of the measurement of the duration of the systolic upstroke of the ACG for the assessment of left heart performance in human subjects; for this purpose the relationship between the mentioned externally measurable time interval in ACG and some of the widely accepted isovolumic indexes of myocardial function[18-20] was explored from high fidelity tracings obtained by means of catheter micromanometers and a pulse transducer with infinite time constant.

Patients

Apexcardiograms were recorded in 74 subjects. All had sinus rhythm. In 54 healthy individuals apex tracings alone were recorded, whereas in the other 20 ACG's were obtained during left heart catheterization. In the catheterized patients premedication consisted of 10 mg. of Librium or 5 mg. of Valium given orally 1 hour before catheterization. The left heart function was examined at rest and during a standardized isometric test (handgrip[21]) as well as in some cases during dynamic exercise.

Group I consisted of 54 normal volunteer subjects with no cardiovascular abnormality on clinical examination or chest roentgenogram, in whom ACG's alone were recorded in order to establish the normal range of the duration of systolic upstroke of the apex tracing and evaluate the possible influence of resting heart rate on this interval.

Group II was made up of nine patients without myocardial or left heart valvular disease, and with no or with only slight pressure or volume loading of the left ventricle: three patients had a small patent ductus arteriosus and one had a small ventricular septal defect (all four patients with a left to right shunt of less than 15 per cent of the pulmonary flow). One patient had a small atrial septal defect (left to right shunt of 35 per cent of the pulmonary flow), one a slight valvular pulmonic stenosis (peak pressure gradient 18 mm. Hg), one a mild form of coarctation of the aorta (peak pressure gradient 9 mm. Hg), one a stenosis of the truncus brachiocephalicus, and one a functional murmur. The left ventricular isovolumic indexes of myocardial function, determined at rest and during handgrip test, were in all patients of this group within normal limits despite the fact that in four of them the left ventricular end-diastolic pressure (Table I) at rest was slightly increased.

Group III comprised 11 patients with myocardial disease, all documented by coronary arteriography. Six patients had nonobstructive cardiomyopathy; four of them had no valvular disease (one had additionally a small patent ductus arteriosus associated with a slight labile arterial

From the Division of Cardiology, Department of Internal Medicine, University of Zurich, Zurich, Switzerland.
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Reprint requests: J. Manolas, M.D., Department of Internal Medicine, Raemistrasse 100, 8091 Zurich, Switzerland.

Table I Summary of patient data

Pt	Age Sex	Diagnosis	HR (min)	SUT (msec)	t-dA /dt (msec)	A/H (%)	LVP (mm Hg)	AoP (mm Hg)	CI (L /min /M²)	ET (msec)	IVCT (msec)	t dP /dt (msec)	Max dP/dt (mm Hg /sec.)	V_{pm} (mL /sec
Group II														
1 S F	20M	FM	48	107	[illegible]	6	105/14	10₅/64/82	4 9	284	59	46	1810	1 31
2 D R	25F	ASD	81	113	—	10	106/8	106/72/ 9	5 0	283	78	55	1780	1 23
3 T L	19F	PDA	83	109	—	11	100/13	100/6 /82	7 1	262	86	62	1360	1 11
4 R E	4?F	PS	77	106	—	10	131/6	131/8?/102	4 1	251	80	54	2070	1 93
5 P S	28M	Coarc	72	106	63	8	129/7	129/83/104	4 6	272	80	59	1980	1 36
6 P L	19F	PDA	71	100	53	7	97/12	97/64/7?	5 3	297	61	49	1560	1 16
7 B L	43F	STB	7?	107	5?	—	148/13	148/81/110	3 1	269	73	64	1710	1 18
8 W U	2 F	VSD	81	111	67	4	106/6	106/77/97	6 1	24	69	66	1380	1 13
9 R L	21M	PDA	63	12?	56	8	10?/16	102/70/84	6 2	284	72	67	1390	1 13
Mean	26		72	109	[illegible]	8	114/11	114/7?/90	5 2	272	74	58	16 0	1 29
±1 S D	±8		±11	±6	±6	±2	±16/±4	±18/±9/±13	±1 2	±17	±12	±7	±260	±0 28
Group III														
10 P V	4?M	CAD	9?	113	—	9	106/10	106/69/83	4 2	?01	91	67	1070	0 87
11 E E	?1M	CAD	76	11?	49	9	129/19	129/90/110	3 3	261	93	71	12?0	0 94
12 J L	54M	CMP AS AI	73	1 0	—	14	150/31	124/91/108	2 8	246	10?	83	8 0	0 51
13 P H	6?M	CMP	59	138	56	30	179/20	179/70/135	2 1	2??	99	8	1070	0 72
14 R C	37M	CMP	56	182	—	11	143/12	143/80/102	2 8	275	112	89	910	0 70
15 L G	3 M	CMP PDA	81	138	54	8	176/8	176/84/1?5	4 4	274	97	77	1330	0 93
16 S U	54M	CMP	76	151	[illegible]	9	144/10	144/90/117	?0	237	119	103	1060	0 88
17 R E	60M	CAD	68	118	54	10	137/10	137/79/108	2 3	255	82	8?	1590	1 12
18 F C	48M	CAD	98	1 7	45	6	130/12	1?0/90/110	3 1	?0	87	81	1760	0 99
19 L B	?3M	CMP MI	67	189	102	5	91/6	91/58/80	?6	229	1?6	108	550	0 61
20 I E	34M	CAD	89	106	62	6	11?/9	112/ 4/83	3 4	217	81	79	1460	1 26
Mean	47		76	140	61	11	136/13	134/80/106	3 0	241	99	84	1170	0 87
±1 S D	±11		±13	±29	±18	±7	±27/±?	±27/±11/ ±18	±0 8	±26	±15	±13	±300	±0 22
P	<0 001		NS	<0 01	NS	NS	NS/NS	NS/NS/NS	<0 001	<0 01	<0 005	<0 001	<0 001	<0 005

Abbreviation
A H = A wave percentage amplitude of ACG
AI = aortic incompetence
AoP = aortic pressure (systolic/diastolic/mean)
AS = aortic stenosis
ASD = atrial septal defect
CAD = coronary artery disease
CI = cardiac index
CMP = nonobstructive cardiomyopathy
Coarc = coarctation of the aorta
ET = ejection time
F = female
FM = functional murmur
HR = heart rate
IVCT = isovolumic contraction time
LVP = left ventricular pressure (systolic/end-diastolic)
M = male
max dP/dt = maximal rate of rise of left ventricular pressure
MI = mitral incompetence
NS = not significant (P>0 05) P values were obtained by unpaired Student's t test
PDA = patent ductus arteriosus
PS = pulmonic valvular stenosis
SD = standard deviation
STB = stenosis of the truncus brachiocephalicus
SUT = systolic upstroke time of ACG
t-dA/dt = time from the onset to the peak of the first derivative of ACG
t-dP/dt = time from the onset to the peak of dP/dt
V_{pm} = peak measured velocity of shortening of the contractile elements
VSD = ventricular septal defect

hypertension and one a moderate arterial hypertension) one had a minimal mitral incompetence (regurgitation fraction 0 03) and one had a slight aortic stenosis (mean pressure gradient by planimetry 15 mm Hg) and aortic incompetence (regurgitation fraction 0 13) Five patients had coronary artery disease two had infarction of the anterior wall and three had three vessel disease

Methods

Apexcardiograms were made with the patient in the left lateral decubitus position usually at an

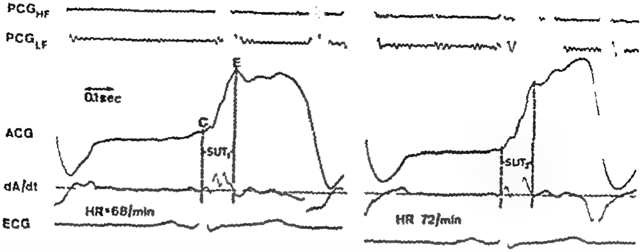


Fig 1 Normal subject simultaneous records of apexcardiogram (ACG) its first derivative (dA/dt) the external apical phonocardiogram (PCG_{HF} = high frequencies PCG_{LF} = low frequencies) and Lead II of the ECG C = onset of ACG upstroke E = summit of the systolic upstroke of ACG HR = heart rate SUT = systolic upstroke time of the ACG Paper speed 200 mm per second By variation of the way of application of the pulse transducer to the chest wall the ACG shows a normal (left panel) or a so called sustained pattern (right panel) in both cases the SUT is identical (SUT_1 = SUT_2) The SUT is measurable as the interval between C and E point of ACG whereas SUT is measurable by the use of dA/dt For further explanation see text

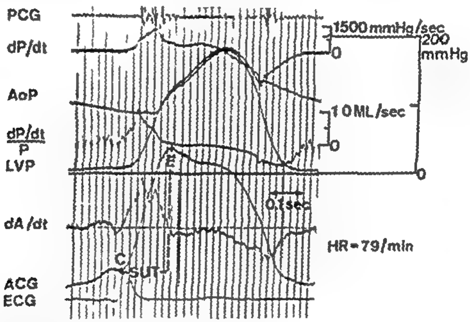


Fig 2 Simultaneous recordings of left ventricular apexcardiogram (ACG) and its first derivative left ventricular pressure (LVP) and its first derivative (dP/dt) aortic pressure (AoP) instantaneous velocity of shortening of the contractile elements (dP/dt)/P the external apical phonocardiogram and Lead II of the ECG from a patient with idiopathic nonobstructive cardiomyopathy and impaired myocardial contractility The systolic upstroke time (SUT) of ACG is prolonged (133 msec)

angle of 20 to 40 degrees whereby the pulse transducer was held by hand at the point of maximal impulse of the apex beat of the heart in healthy persons of Group I apex tracings have been registered in different positions both of the body and of the axis of the transducer in relation to the chest wall, in order to evaluate the possible effects of these positions on time intervals of ACG s The pulse transducer was constructed in our laboratory and consists of a Marey capsule (diameter 2 cm) with the interior surface of this capsule directly connected without air leakage to a Bio Tec transducer (BT 250 T) which has a flat response at frequencies from 0 to 15 000 Hz and an infinite time constant the distance from the transducer to the opening of the capsule mea

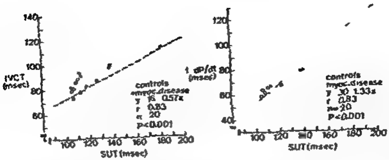


Fig 3 Linear regression analysis between isovolumic contraction time of the left ventricle (*IVCT*) and systolic upstroke time (*SUT*) of the apexcardiogram (left panel) and between time interval from the onset to the peak of the first derivative of left ventricular pressure (*t dP/dt*) and *SUT* (right panel)

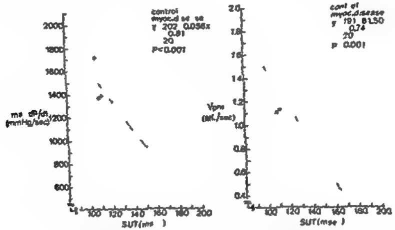


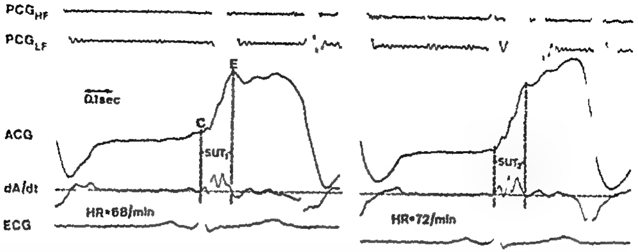
Fig 4 Linear regression analysis between maximal rate of rise of the left ventricular pressure (*max dP/dt*) and systolic upstroke time (*SUT*) of the apexcardiogram (left panel) and between peak measured velocity of shortening of the contractile elements (V_{pm}) and *SUT* (right panel)

sured 0 7 cm Due to its configuration this system had no measurable time delay

Left heart catheterization was performed with the percutaneous transfemoral technique Pressure curves were recorded by Statham SF catheter tip manometers introduced into the left ventricle by the retrograde or transseptal approach and into the ascending aorta by the retrograde route

Analysis of the simultaneous tracings All tracings were recorded on a 16 channel Electronics for Medicine oscillograph (DR 16) at a paper speed of 200 mm per second with time lines of 20 msec In subjects of Group I the ACG and its first derivative (dA/dt) were recorded simultaneously with the external apical phonocardiogram and Lead II of the electrocardiogram (Fig 1) In catheterized patients of Groups II and III there were recorded in addition to the mentioned tracings the left ventricular pressure its first derivative and the instantaneous quotient of the first derivative of left ventricular pressure to total left ventricular pressure (Fig 2) The first derivative of left ventricular pressure (dP/dt) and the instantaneous quotient of this derivative to total left ventricular pressure (dP/dt)/P were obtained by an analogue computer The time constant of the computer for calculating dP/dt and the first derivative of ACG (dA/dt) was 0 8 msec that for calculating (dP/dt)/P was 1 1 msec In addition (dP/dt)/P was calculated manually The peak measured velocity of shortening of the contractile elements (V_{pm}) during the isovolumic phase of the ventricular systole was determined according to the maximal value of (dP/dt)/(P 28) in muscle lengths (ML) per second where 28 is the coefficient of series elasticity

The duration of the isovolumic phase of left ventricular systole (IVCT) was measured from the onset of the rise of the LV pressure curve to



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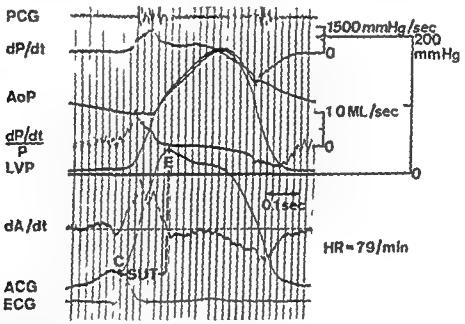

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angle of 20 to 40 degrees whereby the pulse transducer was held by hand at the point of maximal impulse of the apex beat of the heart in healthy persons of Group I apex tracings have been registered in different positions both of the body and of the axis of the transducer in relation to the chest wall, in order to evaluate the possible effects of these positions on time intervals of ACG s The pulse transducer was constructed in our laboratory and consists of a Marey capsule (diameter 2 cm) with the interior surface of this capsule directly connected without air leakage[21] to a Bio Tec transducer (BT 250 T) which has a flat response at frequencies from 0 to 15 000 Hz and an infinite time constant the distance from the transducer to the opening of the capsule mea

simultaneously with the onset of the rise of the left ventricular pressure curve whereby the latter preceded the former by only 4 ± 5 msec ($\pm$ S D) The end of the systolic upstroke of the ACG followed in all cases the onset of the ejection phase of the left ventricle by an interval of 42 ± 18 msec the SUT thus being longer than the isovolumic contraction phase of the left ventricle The mean value of the systolic upstroke time showed no significant difference between Groups I and II this interval averaged in all subjects with normal heart function (pooled Groups I and II) 99 ± 17 msec In contrast the mean value of SUT in group III was 140 ± 29 msec longer than in Group II (109 ± 6 msec) as well as the mentioned value of pooled Groups I and II these differences were significant at the level of $P < 0.01$ and $P < 0.001$ respectively The most important finding of the present study however was the excellent interrelation between SUT of the ACG and the internally measured isovolumic indexes of myocardial performance a close positive correlation (Fig 3) was obtained between SUT and IVCT ($r = +0.83$) as well as with t dP/dt ($r = +0.83$) moreover a close inverse correlation (Fig 4) with max dP/dt ($r = -0.81$) and with V_{pm} ($r = -0.74$) all the mentioned correlations were significant at the level of $P < 0.001$ In contrast there was only a poor but also significant correlation with the cardiac index ($r = -0.53$ $P < 0.01$) and no significant correlation with LVEDP and ejection time of the left ventricle

In this context it must be emphasized that the inverse correlations of IVCT to max dP/dt ($r = -0.78$) and V_{pm} ($r = -0.62$) were also significant ($P < 0.001$) but apparently less strong compared to the above mentioned correlation of SUT with the contractile indexes in contrast the IVCT was more closely correlated with t dP/dt ($r = +0.88$ $P < 0.001$) To evaluate the possible influence of resting heart rate on SUT linear regression analysis of the first variable with the later was carried out in the 63 subjects with normal left heart function (pooled Groups I and II) There was some tendency of SUT to decrease at increasing resting heart rate (Fig 5) however the inverse correlation was very slight although significant ($r = -0.44$ $P < 0.001$) Furthermore the slope of the regression line depicted in Fig 5 was very flat this means that for the interpatient comparison of SUT the influence of resting heart rate as a determinant of contractile state per se has to be accounted for only when heart rate differs greatly

From the 11 patients of Group III only three (Nos 13 14 and 20 in Table I) showed an obliterated E point ("sustained apical impulse") corresponding to 27 per cent of the patients of this group one of these (No 20 in Table I) had normal indexes of myocardial function at rest

Other apexcardiographic parameters The usefulness of two widely accepted parameters in quantitative apexcardiography was also examined in our study

A wave percentage amplitude (A/H ratio) This showed in normal subjects (pooled Groups I and II) a mean value of 9 ± 4 per cent it was only slightly and not significantly increased in Group III (11 ± 7 per cent) Moreover the A/H ratio was poorly correlated with LVEDP in the catheterized patients ($r = +0.51$ $P < 0.01$)

First derivative of apex tracing (dA/dt) This showed a very variable inter and intrapatient configuration in all subjects studied In six of the 64 subjects with normal left heart function (10 per cent) and three of the 11 patients with abnormal left heart function (27 per cent) no sharp peak dA/dt (Fig 1) was recognizable The time from the onset to peak dA/dt (t dA/dt) was also very variable in pooled Groups I and II it averaged 51 ± 12 msec and was not significant different from the mean value of Group III (61 ± 18 msec) furthermore, the t dA/dt showed no significant correlation with any of the mentioned internally measured indexes of myocardial function

Discussion

Review of the literature In recent years the usefulness of different either amplitude or time criteria of quantitative apexcardiography has been examined many authors have sought to correlate these parameters measured externally in the ACG with internal indexes of left ventricular performance

The quantitation of left myocardial function by the use of amplitude parameters[11 13] has not been feasible because of differences among individual subjects in cardiac size and thoracic shape Some authors have examined the relation between the ratio of the A wave to the total amplitude of the ACG (A/H) and LVEDP[13 14] An abnormal increase in the A/H ratio has been

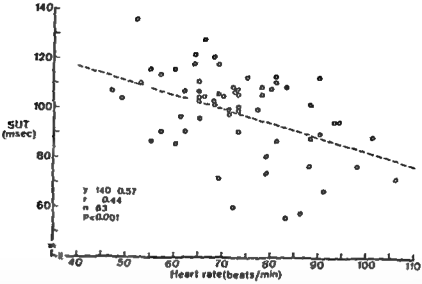

Fig 5 Linear regression analysis between systolic upstroke time (*SUT*) of apexcardiogram and resting heart rate in patients with essentially normal left ventricular function (control subjects without clinical signs of cardiac disease and those catheterized patients without left valvular or myocardial disease and normal contractile indexes at rest and under stress tests) some tendency of SUT to decrease at increasing resting heart rates is demonstrated but the correlation of the two variables is very slight although significant

the point of crossover of LV and aortic pressure curves Also measured were the duration of the LV ejection phase as the time interval from this crossover point to the time when left ventricular pressure fall was at the level of the aortic notch and the time interval from the onset of LV contraction to the peak of dP/dt(t dP/dt)

The following parameters were measured in the apex tracings The duration of the systolic upstroke of the ACG called SUT (systolic upstroke time) was measured from the onset (C point) to the end of the protosystolic upstroke of the ACG In the most cases the later is the so called E point of ACG in other cases however it is difficult to identify precisely either the C or the E point of the ACG An obliterated (sustained) E point can be the result of either impaired myocardial function (see below for further discussion) or of an inadequate way of application of pulse transducer to the chest wall, as demonstrated in Fig 1 In these cases the duration of the systolic upstroke was determined by the use of the first derivative of the ACG as shown in Fig 1 whereby the onset of the upstroke of the ACG is given by the point where dA/dt rises from the baseline and the end of the upstroke by the point where dA/dt, after having reached its maximal value, descends to the zero line of the first derivative Further, the widely accepted parameters in quantitative apexcardiography were measured The ratio of the height of the A wave to the total amplitude (A/H) and the time from the onset to the peak of the first derivative of the ACG (t dA/dt) For each measurement five separate heart cycles were averaged

Results

The individual data obtained for the noninvasive and invasive measurements in catheterized patients of Groups II and III are summarized in Table I There was no significant difference between Groups II and III in the mean values of the heart rate, systolic and diastolic aortic pressures or the left ventricular end diastolic pressure, in contrast the following conventional parameters of left ventricular function were significantly different in these two groups the left ventricular ejection time ($P < 0.01$) isovolumic contraction time ($P < 0.005$), and time from onset to the point of maximal rise (t dP/dt) of left ventricular pressure ($P < 0.001$) further the accepted standards of contractility [4] showed also a significant difference in these two groups the maximal rate of rise of left ventricular pressure ($P < 0.001$) and the peak measured velocity of shortening of the contractile elements ($P < 0.005$)

***The systolic upstroke time** of the ACG* called SUT is defined as the time interval from the onset to the end of the protosystolic wave of the apex tracing The onset of the upstroke of the ACG occurred in all catheterized patients almost

point) followed in all cases the onset of the ejection in the aorta by a mean interval of 42 msec These findings are in contrast to the conclusions of Inoue[25] and Gàbor[32] and their co workers in human subjects and of Willems and co workers in dogs and are in keeping with the findings of Spodick and Kumar[27] and Oreshkov[33] In the present study neither the A wave percentage amplitude nor the time from the onset to the peak dA/dt showed any significant correlation with internally measured indexes of myocardial function One can thus conclude that these accepted criteria in quantitative apexcardiography are not of such great importance as has been widely considered

Summary

In 11 patients with nonobstructive cardiomyopathy and coronary heart disease and decreased myocardial function of the left ventricle as well as in nine patients without left heart valvular or myocardial disease left apexcardiograms were recorded during diagnostic heart catheterization wherein micromanometers were used ACG s were registered additionally in 54 healthy volunteers in order to establish the normal range of apexcardiographic parameters In all cases the apex tracings were recorded by means of a pulse transducer with infinite time constant The most important finding of this study was the close correlation between the duration of the systolic upstroke (SUT) of the apex tracing and some accepted isovolumic indexes of left heart function (isovolumic contraction time time interval from the onset to peak of the first derivative of left ventricular pressure maximal value of the first derivative of left ventricular pressure and the peak measured velocity of shortening of the contractile elements)

Further the mean value of SUT in patients with impaired left myocardial function was significantly prolonged compared to the control subjects an overlap was apparent due to the fact that some of these patients showed a normal left myocardial performance at rest having an abnormal response only to exercise tests

The apexcardiographic SUT can practically always be measured when the first derivative of apex tracing is simultaneously recorded It showed itself to be only slightly influenced by the resting heart rate

The mentioned relationship of the systolic upstroke time of the ACG to internal isovolumic indexes of myocardial function makes this noninvasive measurable parameter an additional excellent tool for the evaluation of the left myocardial state thus supporting a new aspect of the value of quantitative apexcardiography

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described by many authors as being usually associated with severe heart disease[14, 25, 6]

An alternative approach was suggested first by Reale[14] when he reported the similarity in timing and contour between the first derivative of ACG and the left ventricular dP/dt More recently Vetter and associates[17] compared the interval from the onset of ventricular depolarization to the peak of the first derivative of the ACG with hemodynamic and angiographic indexes of myocardial function and found significant correlations

Sutton and associates[11, 12] found frequently a sustained pattern of apical impulse, defined as an apex tracing showing a consistent rise during systole which obliterates the E point" in patients 'with primary myocardial disease or valvular regurgitation and impaired myocardial function', therefore, this pattern was suggested as a valid indicator of poor myocardial function

All these studies which have been performed to evaluate the use of quantitative apexcardiography were conducted either by using conventional recording systems or comparing nonsimultaneous tracings The use of conventional pressure recording systems which means fluid filled catheters with finite time constant and variable and mostly unknown catheter delay times or frequency response[3] as well as pulse transducers with often unknown or too short time constants produces time shifts[9] and distortions in the waveform[23, 29], as a result the recorded apex tracings show a more rapid falling off during systole and exaggerated negative deflections Therefore, neither the correlation between internal and external time parameters nor the use of relative magnitude criteria can be valuable, an accurate comparison of time or amplitude indexes is possible only by employing simultaneously internally and externally similar transducers with infinite time constants and no time delay

Present study The present study establishes the value of the measurement of the systolic upstroke time (= SUT) of the ACG as a noninvasive index of left ventricular performance in human subjects

For this purpose, and in order to avoid the above mentioned instrumental hazards recordings of the ACG and of internal pressure curves were obtained simultaneously during heart catheterization in 20 patients using in both cases strain gauge manometers with direct current input, which have high static sensitivity and high natural frequency, thus being suitable for recording of high fidelity tracings To our knowledge there are no corresponding studies with simultaneous high fidelity tracings in human subjects

The most important finding of this communication consists in the demonstrated close correlation between SUT and some important standard temporal isovolumic indexes of left heart performance (IVCT and t dP/dt), as well as with widely accepted internal contractile indexes (max dP/dt and V_{pm}) Further, SUT was significantly prolonged in the patients with nonobstructive cardiomyopathy or coronary heart disease and decreased myocardial function compared to the normal subjects (of Groups I and/or II), it must be emphasized that there was no significant difference between the three groups of either heart rate or blood pressure and between Groups II and III of LVEDP which as determinants of myocardial function could account for the mentioned significant difference of SUT However, there was an overlap of the mean values of SUT in the mentioned groups this is easily explained by the fact that several patients of Group III did not show severe, in some cases not even manifest signs of impaired myocardial function at rest (82 per cent had a normal value of LVEDP and 27 per cent a normal max dP/dt)

According to our findings SUT can be measured in practically all apex tracings when its first derivative (dA/dt) is simultaneously recorded and taken into account in the described way (as shown in Fig 1) in most cases where a sharp onset of upstroke and E point are present SUT can be measured without using the dA/dt In this context it is noteworthy that according to our experience an unsharp E point or a sustained apical impulse can be the result of an inadequate way of application of the transducer to the chest wall and therefore can be recorded also in healthy subjects (see Fig 1) furthermore, 67 per cent of the patients of Group III showed a normal pattern of apical impulse with sharp E point with a falling off after this point These findings are in contrast to those of Sutton and associates[11, 12]

According to our previous findings as well as in the present study the SUT does not correspond the duration of IVCT because although the onset of rise of the systolic upstroke of the ACG coincides with that of the left ventricular pressure curve the end of SUT (mostly being a sharp E

"New" treatment for chronic intractable congestive heart failure

G E Burch M D
J León Galindo M D
J A Cronvich M S
New Orleans La

Congestive heart failure (CHF) is still one of the most serious illnesses of man and a common cause of death With severe CHF and the associated myocardial disease the heart is unable to meet the demands of the tissues of the body for blood even for the resting state The classical symptomatic physical and hemodynamic manifestations of CHF are too well known to warrant discussion in this report The pathophysiology and the clinical manifestations have been extensively studied for many years throughout the world But some aspects of the pathophysiology of CHF described almost 30 years ago[1] especially the changes in the peripheral circulation venous pressure and venous tone of patients with chronic CHF have been ignored That all peripheral digital blood vessels are constricted and that venous tone is high in patients with CHF have been clearly demonstrated rheoplethysmographically Furthermore peripheral vasodilatation and most importantly general systemic vasodilatation in therapy have been shown over 20 years ago to benefit the patient rapidly and dramatically[3] In fact the therapeutic benefits of aminophylline administered intravenously a common practice for a long time are apparently due largely to peripheral vasodilatation This is probably true of nitroglycerin and other peripheral vasodilator agents as well when used in large doses

This report is concerned with a discussion of the role of the systemic and pulmonary vascular systems in the pathophysiology of congestive heart failure both acute and chronic and the demonstration of the dramatic and impressive effect of acute dilatation of the systemic vascular system especially the venous system on the clinical and physiologic manifestations of chronic intractable congestive heart failure Although this report describes the use of an α adrenergic vasodilating drug in patients with chronic intractable right and left ventricular congestive heart failure the principles apply to acute left and/or right ventricular congestive heart failure as well

Aspects of the pathophysiology of chronic CHF

It is too frequently not realized that the human cardiovascular system consists of two pumps (and even actually a third one—the venous pumping system which is best developed in the skeletal muscles of the extremities) The two pumps (the right and left ventricles) are separated by two vascular systems the systemic and pulmonic The systemic vessels contain approximately 4,500 ml of blood and the pulmonary vessels contain about 500 ml[4] The largest volume of blood is contained in the venous systems[5-7] As indicated previously when the two pumps (right and left ventricles) pump equal amounts of blood the volume of blood in each vascular bed remains constant However if the left ventricle fails and pumps less blood per stroke or per minute than the right ventricle then more blood is pumped into the lungs by the right ventricle than is removed from the lungs by the left ventricle

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From the Department of Medicine of Tulane University School of Medicine and the Charity Hospital of Louisiana New Orleans, La

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Reprint requests G E Burch, M D 1430 Tulane Ave New Orleans, La 7011[illegible]

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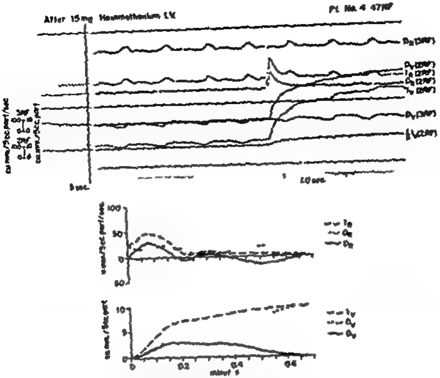

Fig. 1B The curves show marked dilatation of all digital blood vessels in response to intravenous administration of 15 mg of hexamethonium. The drug was injected in 2.5 mg amounts over 9 minutes 5 seconds and this recording was obtained 20 seconds after the final 2.5 mg dose was given. The total digital volume increased 143 cu mm per 5 c.c. part in response to the hexamethonium. The arterial blood pressure decreased from the control value of 142/100 to 118/80 mm Hg.

system. As shown by Eq. (4) of the Appendix, the stress in the wall fibers of an idealized circular cylindrical blood vessel is expressed by

$$S = \frac{pd}{2t}$$

where p is the blood pressure, d is the internal diameter of the vessel, and t is the wall thickness of the vessel. Consequently, for a given volume of wall per unit length of vessel, those vessels with the lower ratios of d_i/t have less wall fiber stress and therefore have a mechanical advantage over those with larger ratios. The small veins in the peripheral vascular bed have lower ratios of d_i/t than the large veins of the lungs and the large systemic central veins, such as those of the neck. Thus when nerve impulses to increase wall stress arrive with equal intensity at all vessels, the small veins and venules (even capillaries) with their mechanical advantage will contract readily, thereby displacing the volume of blood in them, whereas the larger vessels in the lungs and the central systemic vessels of the neck, despite the same and equally intense sympathetic nerve stimuli, are forced to dilate to accommodate the blood forced out of the more peripheral small venous vessels. It may be noted that by contracting, the small vessels have a reduction of d_i/t, thereby increasing their mechanical advantage even more, but the dilated large vessels have an increase of d_i/t, thereby increasing further their mechanical disadvantage.

If the stress inducing impulses are blocked, the resulting relaxation permits the small vessels to return to their normal dimensions and accept the blood which is pumped to them by the left ventricle from the distended larger central veins. In turn, the larger vessels also can return to normal size and become less congested throughout the pulmonary and central systemic venous circulations. The symptoms and signs of CHF would be expected, then, to subside.

Physiologic studies, methods and materials

Five patients with chronic intractable biventricular functional Class IV congestive heart failure were studied. The patients rested in a

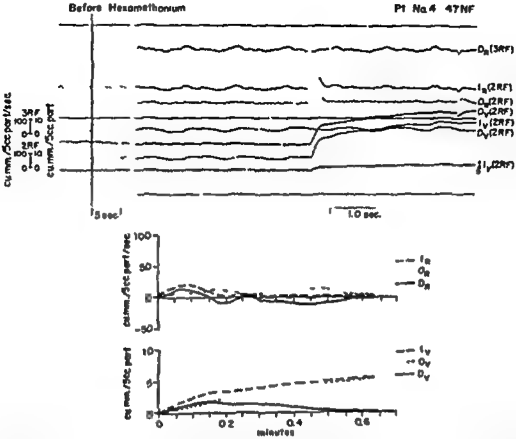

Fig 1A Rheoplethysmograms showing simultaneous time course curves of volumes and rates of digital inflow, outflow and difference between inflow and outflow in a 47 year old patient with severe congestive heart failure. The curves show all digital vessels to be constricted, including the A-V shunts.

Therefore the pulmonary vascular bed becomes congested with blood and the clinical and hemodynamic symptoms and signs of left ventricular CHF ensue.[1] The blood vessels of the lungs cannot accommodate the entire 4,500 ml of blood contained in the systemic blood vessels. On the other hand, should the right ventricle fail to pump as much blood as the left ventricle, then all of the blood in the pulmonary vessels could be pumped into the large systemic vessels, which could readily accommodate the 500 ml and still not become tightly congested.[1] However, with right ventricular CHF the systemic veins are "tight" not because a large volume of blood is "stuffed" into the systemic veins but because of high α adrenergic sympathetic tone. This high sympathetic tone is manifested by the marked vasoconstriction noted rheoplethysmographically in the digital vessels and the high venous pressure revealed in these studies and described subsequently. The reasons or mechanisms responsible for the high α adrenergic sympathetic tone in CHF are unknown. The concept of the two pump system of human circulation is discussed in great detail elsewhere.[1]

When the smooth muscle tone of the systemic veins is increased because of increased α adrenergic sympathetic nerve activity, blood is forced into the lungs and into the central systemic venous system and the right side of the heart (the right pump). This results in distended neck veins, liver distension, pulmonary congestion and many of the manifestations of CHF and even the renal dysfunction associated with increased renal venous pressure and venous congestion of CHF. If venous tone is increased in CHF, then an α adrenergic sympathetic blocking drug should alter this state and should result in improvement of the patient's clinical and physiologic state. This was found to be true and experimental findings and theoretic considerations of such changes are reported and discussed in this paper.

Theoretic hemodynamic considerations

The shift of blood in the vascular system between the small vessels and the lungs and vessels of the neck is related to the hemodynamic phenomena associated with the effects of neural and humoral stimuli on the cardiovascular

Total I /heart beat (cu mm /5 c c part)		Maximal D (cu mm /5 c c part)		Increase in total digital volume (cu mm /5 c c part)
Before C	After C	Before C	After C	
4 7	10.5	2 4	^5	8+
6 5	10 4	4 4	5 0	65
5 5	4.8	2 0	2 1	—
5 6	10 5	1 6	3 2	143
10.2	10 1	2 6	5 0	95
6 5	9 3	2 6	3 6	78+

blood flow showed that all the digital vessels including the A V shunts dilated and that digital inflow and outflow increased markedly (Fig 1B) Total digital volume increased considerably throughout the administration of hexamethonium in all patients indicating the shift of blood from the central systemic vessels to the peripheral vessels As the peripheral dilatation developed the patient improved dramatically

The data varied quantitatively from patient to patient but all the digital vessels were tightly constricted in all the patients with CHF prior to a adrenergic sympathetic nerve blockade The intravenous administration of hexamethonium dilated all digital vessels in all patients No effort was made to quantitate the sensitivity of each patient to the drug or to study digital flow on a statistically quantitative basis in any patient or in the group of patients

Systemic venous pressure Systemic venous pressure measurements obtained with pressure transducers and recorders revealed high pressure in the left forearm vein in all patients in whom it was measured (Table I) The pressure varied from patient to patient and in accordance with the degree of CHF As the hexamethonium was injected systemic venous pressure decreased (Fig 2) simultaneously with digital vasodilatation The degree of all vascular dilatation varied directly with the dosage of hexamethonium administered In fact the degree of vascular dilatation attained was arbitrarily decided for each patient by us The maximum clinical limit definitely was not reached As the systemic venous tone declined and the veins loosened the patient improved clinically and the symptoms and signs of CHF reduced dramatically or disappeared

Central venous pressure The neck veins which reflect changes in central and systemic venous pressure were photographed periodically and watched carefully throughout the investigations Before hexamethonium was injected the neck veins of all patients were markedly dilated and congested with blood even with the patient's back rest elevated (Figs 3 and 4) The distended neck veins reflected high central venous pressure and high right atrial pressure Several patients had marked pulsations in the congested external jugular veins because of tricuspid regurgitation In several patients the veins were turgid to palpation and felt like ropes because their intravenous pressure was so high and their walls so tight Even the veins of the face and forehead were prominent and turgid in some patients reflecting the high venous pressure (Fig 4)

As the hexamethonium injected intravenously into a small vein in the left forearm caused the systemic venous pressure to decrease and the *digital vascular* system to dilate the neck veins decreased in size and became less and less turgid Finally by the time 15 to 17 5 mg of hexamethonium had been administered the neck veins and also the forehead veins became visible (Figs 3 and 4)

Symptomatically, the patient s neck veins felt soft and the patient could rotate his head freely without discomfort previously produced by the distended tight veins in the neck The previous feeling or sensation of intrathoracic fullness tightness or congestion subsided and finally disappeared as the neck veins became less distended and the generalized peripheral vasodilatation developed These symptomatic changes were dramatic and impressive especially the disappearance of the dyspnea breathlessness tightness and fullness in the chest experienced by the patient These changes occurred within 5 to 13 minutes of the initial injection of hexamethonium in all patients

Systemic arterial pressure Before hexamethonium was administered the arterial blood pressure was *not* high in any patient and in a few patients it was impressively low in spite of the peripheral vasoconstriction (Table I) This vascu

Table 1 Influence of hexamethonium chloride (C_6) on venous and peripheral circulations of patients with chronic intractable CHF

Patient No	Age sex	Total C given (ml)	Time for total injection (min)	Heart rate (beats/min)		Arterial pressure (mm Hg)		Systemic venous pressure (mm H_2O)		Basal I_R (cu mm/5 cc part/sec)		Maximal I_R (cu mm/5 cc part/sec)	
				Before C	After C	Before C	After C	Before C	After C_6	Before C	After C_6	Before C	After C
1	58 F	22 5	7 8	80	64	135/85	105/60	293	147	3	25	22	35
2	58 M	22 5	10 0	70	70	160/95	115/70	374	260	6	11	63	80
3	30 M	15 0	3 3	98	100	115/80	115/80	330	–	11	17	35	37
4	47 F	17 5	12 3	93	87	140/110	110/82	375	270	5	26	23	49
5	27 F	12 5	12 8	110	110	96/80	84/62	–	–	25	38	70	88
Mean	44	18 0	9 2	90	86	129/90	106/71	343	226	10	23	43	58

Patient moved too much for measurement

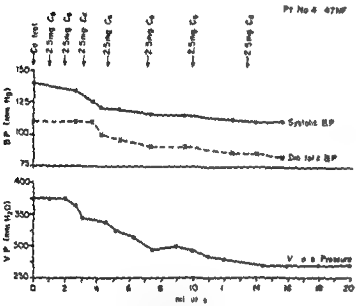

Fig 2 Influence of intravenous hexamethonium on the arterial and systemic venous pressures of the same patient with severe CHF as in Fig 1

comfortable hospital type bed in the neutral environment of our climatic observation room The circulation to and from the right index fingertip (2RF) and the right middle fingertip (3RF) was studied rheoplethysmographically as described previously[a b] with the right arm and hand resting passively with the digits at heart level Systemic venous and arterial blood pressures were recorded with suitable pressure transducers and recorders while the neck veins were closely observed and photographed and the changes in clinical symptoms and signs were carefully noted In some subjects continuous direct recordings of systemic venous pressure and arterial blood pressure were obtained In other subjects changes in venous pressure were noted merely by observing the neck veins and the arterial blood pressure was recorded by means of a clinical mercury type sphygmomanometer

After obtaining baseline measurements and observations, hexamethonium chloride (25 mg per milliliter of concentration) was injected intravenously, 0 1 ml (2 5 mg) at a time, into a vein in the left forearm at intervals of 30 to 120 seconds while the patient was watched carefully and observed for changes in arterial blood pressure systemic venous pressure neck vein distension, digital blood flow, and clinical manifestations of CHF The maximum total amount of hexamethonium injected into any one subject was intentionally limited to 22 5 mg

Results

Peripheral circulation The rheoplethysmograms of all of the patients with CHF showed marked digital vasoconstriction prior to the administration of the hexamethonium (Fig 1A) Basal digital blood flow was also markedly reduced (Fig 1A)[a b] These simultaneous and continuous recordings of volumes and rates of digital inflow and outflow and of differences between inflow and outflow revealed constriction of the arterial and venous vessels of the digits Since the rate of basal flow was also low, the A V shunts were also constricted in the patients with CHF at rest

As the hexamethonium was injected intravenously these simultaneously recorded curves of

during the studies (Table I) This is due in part to the fact that small amounts of hexamethonium were used

Respiration Respiratory rate decreased as the patient's dyspnea became less and his lungs became less congested with blood Breathing became less labored and the sensation of suffocation or breathlessness disappeared as venous pressure decreased and the neck veins became soft The symptomatic improvement progressively occurred concomitantly with the decrease in venous congestion In some patients the crepitant râles in the bases of both lungs decreased in extent and degree and even disappeared

Discussion

The mechanisms and physiologic reasons for the high α adrenergic sympathetic tone and resultant marked peripheral vascular constriction and the general increase in systemic venous tone in patients with congestive heart failure remain unknown That such high vascular tone exists in CHF is obvious from these observations and previous publications[2,3] The theoretic discussions outlined above and in the Appendix indicate the mechanical factors responsible for the shift of blood centrally in CHF including the shift into the pulmonary vascular system which cannot accommodate more than a small volume of the relatively large amount of blood normally present in the systemic venous reservoir of the body This shift of blood is responsible for many of the manifestations of CHF Whether or not the generalized increase in sympathetic tone is responsible in part at least directly or indirectly for the altered renal function with the resultant water and salt retention is also not known That this is so is conceivable however Surely α adrenergic sympathetic nervous system blocking with hexamethonium does initiate immediate symptomatic improvement of the patient and even marked diuresis associated with the return of renal function to normal in some patients The precise mechanisms responsible for this diuresis are also not known The diuresis could be accounted for by the decrease in systemic venous pressure including pressure in the renal veins

The percentage increase in systemic venous pressure was greater than in arterial pressure in the patients studied In fact the arterial blood pressure was only slightly elevated in two patients whereas systemic venous pressure was increased several fold in all four patients in whom it was measured (Table I) Furthermore symptomatic improvement was more directly related to the decrease in venous tone and venous pressure than to the decrease in arterial pressure One patient improved without any change in systemic arterial pressure Venous tone in most patients decreased before arterial pressure decreased

All digital vessels were constricted in the patient studied No measurements were made of the visceral arterial system The hexamethonium decreased the vascular tone and dilated all blood vessels studied including systemic veins all digital vessels and systemic arteries (except in one patient) With the decrease in tone and the dilatation as evidenced by the decrease in arterial blood pressure the decrease in systemic venous pressure and collapse of the neck veins the patient improved symptomatically One patient had such markedly distended tight neck veins that she was unable to rotate her head without considerable discomfort and fear that she might rupture a neck vein (Fig 3) With the collapse of the neck veins following administration of hexamethonium the ability to rotate her head freely and comfortably was most impressive to her Diuresis developed in the patients and the crepitant râles in the bases of both lungs decreased in extent and amount or even disappeared These changes all suggested that there was preferential increase in venous tone in these patients with CHF in association with an increase in digital vascular tone The precise reasons for such an increase in venous tone in chronic CHF which was readily interrupted with the α adrenergic sympathetic blocking agent are unknown but the increased tone is extremely important in the clinical and physiologic syndrome of CHF The physiologic and hemodynamic contributions of the high venous tone to the production of the clinical manifestations of CHF need to be studied extensively The elevated venous tone and venous pressure may be a cause in large part for the change in renal function which results in electrolyte and water retention in CHF The subtle changes in renal function that generalized increase in venous tone and the resultant venous hypertension produce have received little attention Surely, renal venous pressure must be increased in CHF along with the generalized increase in systemic venous pressure

Hexamethonium decreased systemic venous

Fig 3 Influence of intravenous hexamethonium on the neck veins of the 47 year old patient with severe CHF The hexamethonium (15 mg) was administered in 2 5 mg amounts over 12 3 minutes

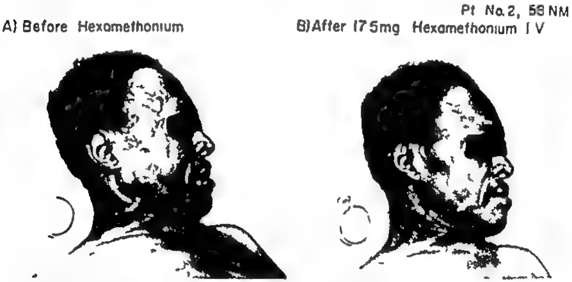

Fig 4 Influence of intravenous hexamethonium on the neck and forehead veins of a 58 year old patient with severe CHF The hexamethonium (17 5 mg) was administered in 2 5 mg amounts over 10 minutes

lar state resembled somewhat the manifestations of impending or mild cardiogenic shock Although arterial pressure was reduced by the hexamethonium to relatively low levels, even to 84/62 in one patient the patients felt much better and were able to stand and walk and sit without syncopal symptoms To avoid excessive vasodilatation the decrease in arterial blood pressure was used as a guideline to discontinue administration of hexamethonium The blood pressure continued to decrease slightly for 5 to 10 minutes after administration of the drug was stopped Because of the effect on blood pressure the drug was administered in 0 1 ml (2 5 mg) amounts at a time, with 30 to 120 second intervals to allow its full effects to occur before administration of the next 0 1 ml

It was not necessary for the arterial pressure to decrease for the patients to feel better or improve clinically as in the case of Patient No 3 (Table I) Improvement seems to be definitely more closely related to the reduction in peripheral venous tone (noted rheoplethysmographically) and to the *decline in systemic venous pressure* (and in pulmonary venous pressure, not observed directly) than to the decrease in arterial blood pressure

Heart rate Heart rate changed very little

during the studies (Table I) This is due in part to the fact that small amounts of hexamethonium were used

Respiration Respiratory rate decreased as the patient s dyspnea became less and his lungs became less congested with blood Breathing became less labored and the sensation of suffocation or breathlessness disappeared as venous pressure decreased and the neck veins became soft The symptomatic improvement progressively occurred concomitantly with the decrease in venous congestion In some patients the crepitant râles in the bases of both lungs decreased in extent and degree and even disappeared

Discussion

The mechanisms and physiologic reasons for the high α adrenergic sympathetic tone and resultant marked peripheral vascular constriction and the general increase in systemic venous tone in patients with congestive heart failure remain unknown That such high vascular tone exists in CHF is obvious from these observations and previous publications [3] The theoretic discussions outlined above and in the Appendix indicate the mechanical factors responsible for the shift of blood centrally in CHF including the shift into the pulmonary vascular system which cannot accommodate more than a small volume of the relatively large amount of blood normally present in the systemic venous reservoir of the body This shift of blood is responsible for many of the manifestations of CHF Whether or not the generalized increase in sympathetic tone is responsible in part at least directly or indirectly for the altered renal function with the resultant water and salt retention is also not known That this is so is conceivable however Surely α adrenergic sympathetic nervous system blocking with hexamethonium does initiate immediate symptomatic improvement of the patient and even marked diuresis associated with the return of renal function to normal in some patients The precise mechanisms responsible for this diuresis are also not known The diuresis could be accounted for by the decrease in systemic venous pressure including pressure in the renal veins

The percentage increase in systemic venous pressure was greater than in arterial pressure in the patients studied In fact the arterial blood pressure was only slightly elevated in two patients whereas systemic venous pressure was increased several fold in all four patients in whom it was measured (Table I) Furthermore symptomatic improvement was more directly related to the decrease in venous tone and venous pressure than to the decrease in arterial pressure One patient improved without any change in systemic arterial pressure Venous tone in most patients decreased before arterial pressure decreased

All digital vessels were constricted in the patient studied No measurements were made of the visceral arterial system The hexamethonium decreased the vascular tone and dilated all blood vessels studied including systemic veins all digital vessels and systemic arteries (except in one patient) With the decrease in tone and the dilatation as evidenced by the decrease in arterial blood pressure the decrease in systemic venous pressure and collapse of the neck veins the patient improved symptomatically One patient had such markedly distended tight neck veins that she was unable to rotate her head without considerable discomfort and fear that she might rupture a neck vein (Fig 3) With the collapse of the neck veins following administration of hexamethonium the ability to rotate her head freely and comfortably was most impressive to her Diuresis developed in the patients and the crepitant râles in the bases of both lungs decreased in extent and amount or even disappeared These changes all suggested that there was preferential increase in venous tone in these patients with CHF in association with an increase in digital vascular tone The precise reasons for such an increase in venous tone in chronic CHF which was readily interrupted with the α adrenergic sympathetic blocking agent are unknown but the increased tone is extremely important in the clinical and physiologic syndrome of CHF The physiologic and hemodynamic contributions of the high venous tone to the production of the clinical manifestations of CHF need to be studied extensively The elevated venous tone and venous pressure may be a cause in large part, for the change in renal function which results in electrolyte and water retention in CHF The subtle changes in renal function that generalized increase in venous tone and the resultant venous hypertension produce have received little attention Surely renal venous pressure must be increased in CHF along with the generalized increase in systemic venous pressure

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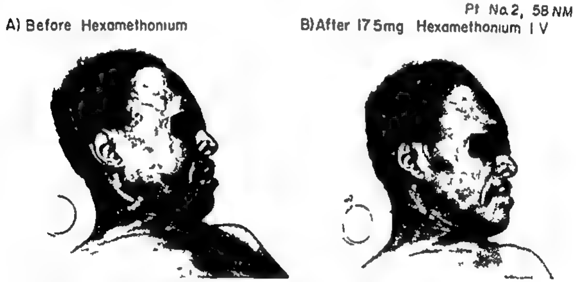

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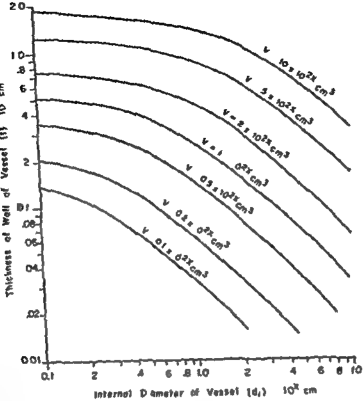

Fig 6 Wall thickness (t) vs internal diameter (d_i) as a function of wall volume per centimeter length (V). With the selection of the exponent x for dimensions of d, t and V, these curves apply to a wide range of dimensions.

chambers central venous pressure pulmonary arterial or venous pressure ejection rate or other hemodynamic phenomena for fear that the methods used would complicate the studies Furthermore these measurements were not necessary The plan was to employ simple methods for monitoring the physiologic and clinical state during the administration of hexamethonium since physicians in hospital and emergency room practice should be able to employ the drug effectively under practical and simple circumstances

The role of the decrease in arterial blood pressure in improving the state of CHF is not clearly evident from these studies It must have been a contributing factor but not a necessary one nor the most important one certainly not as important as the decrease in systemic venous and peripheral vascular tone This was evident from patients with CHF in whom arterial blood pressure was already low and the systemic venous pressure extremely high Also venous pressure decreased in some patients initially with injection of the hexamethonium with definite symptomatic improvement even though arterial blood pressure had not changed or had decreased minimally Apparently the clinical improvement in the state of CHF was due to the decline in systemic venous pressure and a shift of blood from the pulmonary blood vessels especially the pulmonary veins and central veins Furthermore merely a decrease in load on the left ventricle without a decrease in α adrenergic sympathetic nervous system tone would not produce a decrease in systemic venous tone

The mechanical disadvantage under which the large central veins function as compared to the smaller more peripherally located ones which contain most of the blood is readily shown by the Appendix and Figs 5 6 and 7 The relative intensity of α adrenergic sympathetic nerve impulse stimulation for different size veins is yet to be determined For example is the intensity of sympathetic nerve stimulation the same per unit volume of venous wall or per smooth muscle cell or per unit cross sectional area of all vessels?

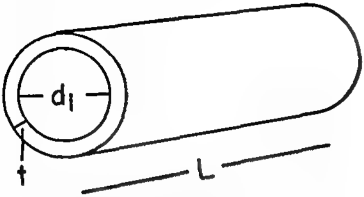

Fig 5 The idealized cylindrical vessel used in calculations in the Appendix of wall volume and wall fiber stress

tone so that the large systemic venous vessels relaxed or loosened and accommodated a large volume of blood under lower pressure as the left ventricle pumped blood into the peripheral vascular system from the pulmonary vascular system When the left ventricle pumped more blood out of the lungs than the right ventricle pumped into the lungs a new state of equilibrium resulted in which there was less blood in the pulmonary venous and entire pulmonary vascular system and in the large central systemic veins but more blood in the smaller peripheral vessels with all intravenous blood pressure being at lower levels The distribution of blood in the circulation became more normal The pressure in the pulmonary vascular system must have been reduced because blood volume in that system was reduced whereas the pressure in the systemic venous system was reduced, in spite of an increase in its blood volume because of the decrease in venous tone produced by blocking of the α adrenergic sympathetic nervous system In the management of CHF by venesection, the volume of blood is reduced in the systemic veins which reduces the wall stress on these veins but the α adrenergic sympathetic nervous system tone and in turn, the smooth muscle tone of the venous walls are not reduced even indirectly

Increase in venous tone is the direct cause for the elevated venous pressure due to high sympathetic nerve stimulation of veins and in turn accounts for the venous congestion of CHF However, hexamethonium interrupts the direct cause for high venous tone by blocking the α adrenergic sympathetic nervous system tone Thus the patient is bled into his systemic veins, and blood is redistributed to achieve a more normal distribution of blood volume with a more normal venous and sympathetic nervous tone vessel wall tone and intravascular pressure The pharmacologic and physiologic procedure employed to achieve this state was simple The patients felt better Respiration was improved The associated decrease in arterial blood pressure unloaded the heart, and its function apparently improved Hexamethonium then, really provides, by physiologic readjustments, intravascular venesection without blood loss The latter point is especially important if the patient is anemic This procedure and drug can be used readily clinically in the care of patients with CHF

It should be clearly indicated that hexamethonium is most effective when systemic venous pressure is elevated and the lungs are congested with blood This is evident from previous discussions of the mechanisms of CHF[1] and recent unpublished studies Thus this vasodilator would be most effective in patients whose CHF is progressively getting worse or in whom the CHF has reached a stable state as with intractable severe CHF

Hexamethonium is the best vasodilator and α adrenergic sympathetic blocking agent available today for clinical use for the relief of CHF as described above It acts rapidly so that the physician can judge when he has administered the proper dose intravenously The full effect is reached in 2 to 3 minutes after injection Furthermore its action subsides rapidly The resultant vasodilatative effects may linger totally or in part for hours or days even though the drug itself has ceased to be present When hexamethonium is used properly norepinephrine its antidote should never be needed to correct an overdose of hexamethonium The dose of hexamethonium can be carefully and accurately monitored at the bedside for each patient by observing the changes in arterial blood pressure neck vein distension, and the patient s general state of well being as noted above Thus, the dosage used by us arbitrarily varied according to the patient s response

These studies were not undertaken to quantitate the degree of vascular change produced in CHF by hexamethonium Although the measurements were quantitative the objective was to learn the physiologic changes produced and their effects on the physiologic and clinical state of CHF and the final clinical well being of the patient No effort was made to measure cardiac output end diastolic pressure in the four cardiac

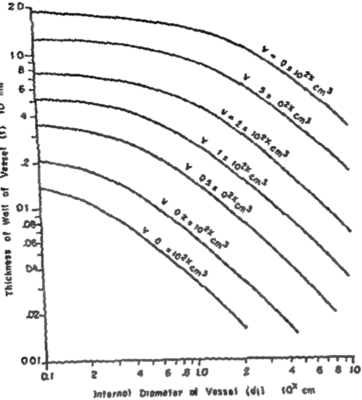

Fig. 8. Wall thickness (*t*) vs. internal diameter (*d*$_i$) as a function of wall volume per centimeter length (V_w). With the selection of the exponent *x* for dimensions of *d*, *t*, and *V*, these curves apply to a wide range of dimensions.

chambers, central venous pressure, pulmonary arterial or venous pressure, ejection rate, or other hemodynamic phenomena for fear that the methods used would complicate the studies. Furthermore, these measurements were not necessary. The plan was to employ simple methods for monitoring the physiologic and clinical state during the administration of hexamethonium since physicians in hospital and emergency room practice should be able to employ the drug effectively under practical and simple circumstances.

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The mechanical disadvantage under which the large central veins function as compared to the smaller, more peripherally located ones which contain most of the blood is readily shown by the Appendix and Figs. 5, 6, and 7. The relative intensity of α adrenergic sympathetic nerve impulse stimulation for different size veins is yet to be determined. For example, is the intensity of sympathetic nerve stimulation the same per unit volume of venous wall or per smooth muscle cell or per unit cross sectional area of all vessels?

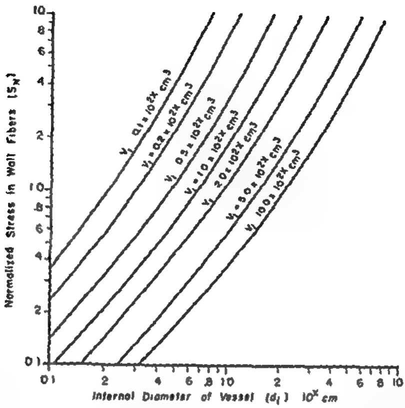

Fig 7 Normalized stress (S_x) vs internal diameter (d_i) as a function of wall volume per centimeter length (V_1) With the selection of the exponent x for the dimensions of d_i and V_1 these curves apply to a wide range of dimensions

Such questions need to be answered for better appreciation of the role or importance of venous tone for the various veins of the body Regardless the relative mechanical state of tension and force of the various veins of the body must be related more or less as described above and indicated by Figs 6 and 7 Surely in order for the changes noted to occur the blood is shifted to the more peripherally located systemic veins because hexamethonium blocks the α adrenergic sympathetic nervous system

The value of hexamethonium in the treatment of chronic intractable CHF and acute pulmonary edema is evident from the clinical response alone All patients with CHF improved immediately and impressively following administration of hexamethonium Several hours after the effects of the drug disappeared some of the patients with chronic and intractable CHF gradually developed dyspnea and central systemic venous and pulmonary congestion again However the level of discomfort was less than that prior to administration One of the patients included in this study was so relieved by the hexamethonium that she requested repeat studies in order to receive the hexamethonium injections An injection can be given daily or even more frequently when the drug is used primarily for clinical care Some patients developed a good diuresis immediately following the use of the drug This response certainly indicates that renal functional state was potentially good and was hemodynamically related to the functional state of the cardiovascular system during CHF since hexamethonium is not a diuretic known to act directly as such on the renal parenchyma We would suggest that the renal dysfunction in these patients with chronic CHF was due in large part to the increase in sympathetic nervous system tone and high renal venous pressure

The procedure for administering hexamethonium clinically is simple and can be employed at the bedside or in the emergency room with only the use of a sphygmomanometer along with careful clinical observations and understanding

Summary

The use of hexamethonium injected intravenously in successive 2.5 mg doses resulted in α adrenergic sympathetic nerve blocking and associated peripheral vasodilatation with dramatic improvement of the symptoms and signs in

patients with marked chronic intractable CHF The vasodilatating effect of the drug is simple to monitor at the bedside and serves as an effective, simple means to bleed the patient intravenously by decreasing systemic venous tone and reducing the wall stress in the vessels This intravenous bleeding results in a shifting of excessive blood from the lungs and central systemic venous areas to the larger volume of the more peripheral systemic venous reservoirs Rheoplethysmographic recordings of digital blood flow in the fingertips of the patients revealed marked constriction of all vessels of the fingers during CHF Hexamethonium dilated all these vessels and increased digital blood flow even though arterial blood pressure was reduced by the drug

Theoretic discussions of aspects of the mechanism of congestive heart failure of the two pump system of the heart of man and the mechanical or hemodynamic advantages of the small veins over the larger centrally located veins tend to explain why the use of hexamethonium benefits the circulation by producing venodilatation These studies indicate the therapeutic usefulness of hexamethonium in the management of acute and chronic intractable CHF and provides physiologic and theoretic data to explain why the drug is effective

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Appendix

Because of the shift of blood volume in the cardiovascular system in pathologic states it is of interest to know the relations between the pressure in the vessels of the cardiovascular system and the radial force on and the stress in the wall fibers of the respective vessels The following analysis is based on an idealized circular cylindrical vessel with walls which are homogeneous radially and which do not elongate axially Thus it is assumed that a change in internal diameter (d_i) is accompanied by an appropriate change in wall thickness (t) to keep constant the volume of wall per unit length (V_1) of vessel

In the cylindrical vessel of Fig 5 the volume of wall

$$
\begin{aligned}
V &= \pi\left[\left(\frac{d_i}{2} + t\right)^2 - \left(\frac{d_i}{2}\right)^2\right]L \\
&= \pi\left[\frac{d_i^2}{4} + d_i t + t^2 - \frac{d_i^2}{4}\right]L \\
&= \pi\left[d\,t + t^2\right]L
\end{aligned} \tag{1}
$$

or V_1 (volume per unit length) $= \pi\,(d_i t + t^2)$

$$\text{Therefore } d = \frac{\frac{V_1}{\pi} - t^2}{t} = \frac{V_1}{\pi t} - t$$

$$\text{or} \qquad t = \frac{-d + \sqrt{d^2 + \frac{4V_1}{\pi}}}{2} \tag{2}$$

The radial force per unit length on the wall produced by fluid at pressure p is

$$F = p\pi d \tag{3}$$

and the stress in the wall fibers is

$$S = \frac{pd\,L}{2tL} = \frac{pd_i}{2t} \tag{4}$$

If V_1 is constant as d changes then

$$S = p\,\frac{d}{2\left[\dfrac{-d + \sqrt{d^2 + \frac{4V}{\pi}}}{2}\right]} = \frac{p}{-1 + \sqrt{1 + \frac{4V}{\pi d}}}$$

Normalizing F and S for p = 1 results in

$$F_N = \pi d$$

and
$$S_N = \frac{1}{-1 + \sqrt{1 + \dfrac{4V_1}{\pi d_i^2}}}$$

If a consistent set of units is used in which

d_i = internal diameter of vessel in centimeters

t = wall thickness in centimeters

L = length of vessel in centimeters

p = pressure in dynes per square centimeter

then V = volume in cubic centimeters

V_1 = volume in cubic centimeters per centimeter length

F = radial force on centimeter length of wall in dynes

S = stress in wall fibers in dynes per square centimeter

S_N = normalized wall stress

For convenience in relating V_1, d_i, and t the curves in *Figs 6 and 7 are given*

These curves are useful over a wide range of internal diameters (d_i) and wall volumes per unit length (V_1) by appropriately selecting the exponent x For example from Fig 6, if x = 0, (a) when $d_i = 2$ cm $= 2 \times 10^0$ cm and $V_1 = 5$ cm^3 $= 5 \times 10^0$ cm^3, $t = 0.61$ cm $= 0.61 \times 10^0$ cm, and (b) when $d_i = 5$ cm and $V_1 = 5$ cm^3 $t = 0.30$ cm But if $x = -5$, then corresponding to (a) above $d_i = 2 \times 10^{-5}$ cm, $V_1 = 5 \times 10^{-10}$ cm, and $t = 0.61 \times 10^{-5}$ cm Similarly, from Fig 7 *the normalized wall stress* (S_N) can be determined In this case whether $x = 0$ or -5 for dimensions given for (a), $S_N = 1.64$ and for dimensions for (b), $S_N = 8.33$ The actual wall stress is expressed by $S = p \times S_N$ Therefore, for the dimensions of case (a) a venous pressure of approximately 100 mm of water ($p = 10\,000$ dynes per square centimeter) would result in a wall stress $S = p \times S_N = 10{,}000 \times 1.64 = 16{,}400$ dynes per square centimeter, whereas for a venous pressure of approximately 400 mm of water ($p = 40{,}000$ dynes per square centimeter) $S = 40\,000 \times 1.64 = 65\,600$ dynes per square centimeter The rapid increase in S_N as d_i increases with constant V_1 is shown by the curves and by the example just considered—an increase of d_i by the factor 5/2 or 2.5 results in an increase of S_N by the factor 8.33/1.64 or 5.07

Therapeutic implications of diazepam in patients with elevated left ventricular filling pressure

Pierre Coté M D
Lucien Campeau M D
Martial G Bourassa M D
Montreal Quebec Canada

In a recent study from this laboratory a reduction in left ventricular end diastolic pressure was observed following intravenous administration of diazepam to patients undergoing cardiac catheterization for diagnostic purposes This was associated with a slight but significant fall in aortic pressure and a decreased left ventricular oxygen consumption From these results we concluded that the drug could lead to an improvement in cardiac function Since these effects were also noted in some patients with hemodynamic evidence of left ventricular failure we purposely elected to investigate further the therapeutic implications of diazepam in patients with elevated left ventricular end diastolic pressure

Methods

Patients Twenty one consecutive patients clinically suspected of having coronary artery disease and undergoing complete evaluation were considered for inclusion in the present study Patients with associated valvular heart disease anemia diabetes and significant pulmonary disease were excluded Drugs such as digitalis beta blocking agents and other cardiotropic drugs were withheld for a period of at least 24 hours before the hemodynamic investigation Patients were selected at the time of left heart catheterization on the basis of an abnormal (greater than 14 mm Hg) resting left ventricular end diastolic pressure Nine patients did not meet this requirement and were rejected from the study Therefore 12 patients form the basis of this report Table I summarizes the clinical and biologic data of these patients Age varied from 49 to 62 with a mean of 55 years The extent of functional disability related to heart failure was graded for each patient according to the New York Heart Association criteria Three patients were in Class III or IV and two of these both with normal coronary arteries were diagnosed as having a congestive type of cardiomyopathy The remaining nine patients were in Class I or II most of them being under medical treatment with digitalis and/or diuretics prior to the investigative procedure Seven patients had moderate to severe left ventricular dysfunction as determined on the left ventriculogram and five patients had a normal left ventricular contraction Three of these five patients however had arterial hypertension with a diastolic blood pressure equal to or greater than 100 mm Hg in addition to coronary artery disease In these five patients the elevated resting left ventricular end diastolic pressure probably reflected changes in ventricular compliance secondary to ischemia and/or hypertrophy resulting from hypertension rather than true left ventricular failure

Procedures All patients were studied after an overnight fast and without premedication Informed consent was obtained prior to the procedure and patients were not given detailed information concerning the nature of the drug to be administered

The drug study was undertaken after coronary

From the Montreal Heart Institute and the Department of Medicine University of Montreal Faculty of Medicine Montreal Quebec Canada.

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Reprint requests Martial G Bourassa M D Montreal Heart Institute 5000 E. Belanger St., Montreal H1T 1C8, Quebec Canada

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and $$S_N = \frac{1}{-1 + \sqrt{1 + \frac{4V_l}{\pi d_i^2}}}$$

If a consistent set of units is used in which

d_i = internal diameter of vessel in centimeters
t = wall thickness in centimeters
L = length of vessel in centimeters
p = pressure in dynes per square centimeter
then V = volume in cubic centimeters
V_l = volume in cubic centimeters per centimeter length
F = radial force on centimeter length of wall in dynes
S = stress in wall fibers in dynes per square centimeter
S_N = normalized wall stress

For convenience in relating V_l, d_i, and t the curves in Figs 6 and 7 are given

These curves are useful over a wide range of internal diameters (d_i) and wall volumes per unit length (V_l) by appropriately selecting the exponent x. For example, from Fig 6 if $x = 0$ (a) when $d_i = 2$ cm $= 2 \times 10^{0}$ cm and $V_l = 5$ cm^3 $= 5 \times 10^{0}$ cm^3, $t = 0.61$ cm $= 0.61 \times 10^{0}$ cm, and (b) when $d_i = 5$ cm and $V_l = 5$ cm^3, $t = 0.30$ cm. But if $x = -5$ then corresponding to (a) above, $d_i = 2 \times 10^{-5}$ cm, $V_l = 5 \times 10^{-10}$ cm and $t = 0.61 \times 10^{-5}$ cm. Similarly from Fig 7 the normalized wall stress (S_N) can be determined. In this case whether $x = 0$ or -5 for dimensions given for (a), $S_N = 1.64$ and for dimensions for (b) $S_N = 8.33$. The actual wall stress is expressed by $S = p \times S_N$. Therefore, for the dimensions of case (a) a venous pressure of approximately 100 mm of water (p = 10,000 dynes per square centimeter) would result in a wall stress $S = p \times S_N = 10\,000 \times 1.64 = 16\,400$ dynes per square centimeter, whereas for a venous pressure of approximately 400 mm of water (p = 40 000 dynes per square centimeter), $S = 40\,000 \times 1.64 = 65\,600$ dynes per square centimeter. The rapid increase in S_N as d_i increases with constant V_l is shown by the curves and by the example just considered—an increase of d_i by the factor 5/2 or 2.5 results in an increase of S_N by the factor 8.33/1.64 or 5.07

Table II. Hemodynamic and metabolic effects of diazepam in patients with elevated resting left ventricular end-diastolic pressure*

	HR (b.p.m.)	*MAP* (mm Hg)	*LVEDP* (mm Hg)	*CI* (L/min/M²)	*LVSWI* (gm M/beat/M²)	*SEP* (msec/beat)	*TTI* (mm Hg/sec/min)	*LVO₂ cons* (ml/min)	*CSBF* (ml/min)	*CVR* (mm Hg/ml/min)	*LVO₂ ext* (%)	*LV lact ext* (%)
Control	8[illegible] ± [illegible]	116 ± [illegible]	24.3 ± 2.9	3 ± [illegible]	58 ± [illegible]	297 ± 7	3060 ± 215	1[illegible]9 ± 13	135 ± 1[illegible]	0.97 ± 0.1	6[illegible] ± [illegible]	21 ± [illegible]
Diazepam 5 min	81 ± [illegible]	107 ± 5	16 ± 2.1	3 ± 0.3	54 ±	282 ± 8	[illegible]76 ± 235	148 ± 17	129 ± 14	0.96 ± 0.1	66 ± 3	16 ± [illegible]
P value	NS	<0.001	<0.001	NS	NS	<0.002	<0.002	NS	NS	NS	NS	NS
Diazepam 15 min	[illegible] ± [illegible]	105 ± [illegible]	15.8 ± 2.1	2.9 ± 0	53 ± 6	288 ± 7	2,6[illegible] ± 2[illegible]3	145 ± 14	129 ± 14	0.90 ± [illegible]	6[illegible] ± 2	[illegible]1 ± 4
P	NS	<0.001	<0.002	NS	NS	<0.0[illegible]	<0.001	NS	NS	NS	NS	NS
			26.7 ± 3.2† (NS)									

Abbreviations: HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; CI, cardiac index; LVSWI, left ventricular stroke work index; SEP, systolic ejection period; TTI, tension-time index; LVO₂ cons, left ventricular oxygen consumption; CSBF, coronary sinus blood flow; CVR, coronary vascular resistance; LVO₂ ext, left ventricular oxygen extraction; LV lact ext, left ventricular lactate extraction.
†Two minutes after left ventricular angiogram.

There was no change in heart rate. Mean arterial pressure decreased an average of 9 to 11 mm Hg (panel *A* of Fig. 1). This was comparable to data observed in previous reports.[4] This fall in mean arterial pressure occurred in all patients and did not require therapy. Systemic vascular resistance decreased from 1,754 ± 100 dynes/sec./cm[-5] in the control state to 1,633 ± 95 and 1,656 ± 78 at 5 and 15 minutes, respectively; however, these changes were not significant. Indirect indices of left ventricular performance such as cardiac index and left ventricular stroke work index were unchanged after diazepam. Cardiac index was below 2.5 L./min./M.² in four patients, three of whom were in functional Class III or IV. It increased in two and remained unchanged in two. *In addition to the fall in arterial blood pressure*, left ventricular end-diastolic pressure, systolic ejection period, and tension time index all decreased significantly at 5 and 15 minutes after the administration of diazepam.

Diazepam induced a significant decrease in left *ventricular end-diastolic pressure* (LVEDP) from 24.3 ± 2.9 mm Hg at rest to 16 ± 2.1 at 5 minutes ($p < 0.001$) and 15.8 ± 2.1 at 15 minutes ($p < 0.002$) (panel *B* of Fig. 1). LVEDP remained unchanged in only one patient. This reduction of LVEDP was still evident (*16.1 ± 2 mm Hg*) before left ventricular angiography approximately 30 minutes after the administration of diazepam. LVEDP recorded 2 minutes after left ventricular angiography increased to 26.7 ± 3.2 mm Hg, a value not significantly different from the pre-diazepam control value (24.3 ± 2.9 mm Hg).

Table III. Respiratory effects of diazepam in patients with elevated resting left ventricular end-diastolic pressure*

	RR (breaths/min)	*Alv vent* (L/min)	*Body O₂ cons* (c.c./min)
Control	15.6 ± 1.3	6.9 ± 0.3	230 ± [illegible]
Diazepam 12 min.	16 ± 1.4	6 ± 0.3	217 ± 6
P value	NS	<0.005	<0.001
	ApH	*ApCO₂* (mm Hg)	*ApO₂* (mm Hg)
Control	7.46 ± 0.01	25 ± 1	71 ± 4
Diazepam 5 min.	7.43 ± 0.01	29 ± 2	62 ± 3
P	<0.05	<0.05	<0.05
Diazepam 15 min	7.46 ± 0.01	26 ± 1	68 ± 3
P	NS	NS	NS

Abbreviations: RR, respiratory rate; Alv vent, alveolar ventilation; body O₂ cons, body O₂ consumption; A, arterial.

Systolic ejection period (panel *C* of Fig. 1) was 297 ± 7 msec at rest and decreased to 282 ± 8 at 5 minutes ($p < 0.002$) and 288 ± 7 at 15 minutes ($p < 0.05$).

Tension time index (panel *D* of Fig. 1), a rough estimate of myocardial oxygen consumption, decreased from 3,060 ± 215 mm Hg/sec./min. at

Table I Clinical and laboratory data

Clinical data	
No	12
Age range (mean)	49 62 (55)
Male female ratio	8 4
Heart failure	
I	8
II	1
III	2
IV	1
Laboratory data	
ECG	
Old myocardial infarct	4
Left bundle branch block	2†
Ischemia no infarct	6
Coronary vessels	
Vessels with 60 per cent obstruction or more	10
Normal anatomy†	2
Left ventriculography	
Abnormal contraction	7
Normal contraction	5

Functional classification of the N Y H A
†These two patients had an idiopathic myocardiopathy

sinus and left heart catheterization and prior to left ventriculography and coronary angiography At least 10 minutes after all catheter manipulations pressures were recorded, blood samples were collected from central aorta and mid coronary sinus, and coronary sinus blood flow and cardiac output were measured These determinations were obtained successively within a period of 3 to 5 minutes Expired air was collected simultaneously for determination of body O_2 consumption Diazepam in a dosage of 0 1 mg per kilogram of body weight was then injected over a 1 minute period via an arm vein through the side arm of an infusion tubing The patients were unaware of the time of drug administration All measurements were repeated twice, between 5 and 10 minutes and between 15 and 20 minutes after diazepam infusion Body O_2 consumption was measured between the twelfth and fifteenth minute during this period Approximately 30 minutes after the drug infusion, the angiographic procedures were carried out

Hemodynamic techniques and measurements The methods used for measurement of aortic and left ventricular pressures, coronary sinus and systemic blood flows and for biochemical determinations have been previously described [1] Pressures were amplified and recorded on high and normal sensitivity and at paper speed of 100 mm

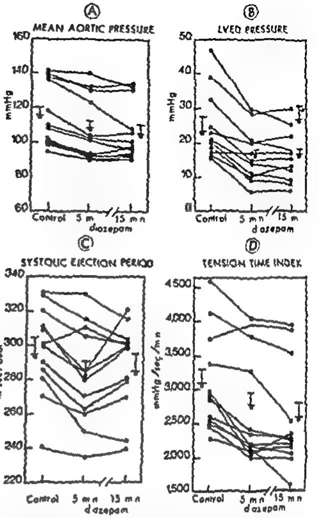

Fig 1 Effects of diazepam on mean aortic pressure (panel *A*) left ventricular end diastolic (LVED) pressure (panel *B*) systolic ejection period (panel *C*) and tension time index (panel *D*) in patients with elevated LVED pressure at rest Mean values ± S E M are shown The asterisk ( ) on panel *B* represents mean LVED pressure 2 minutes after left ventriculography

per second Pressures and systolic ejection period readings were always the mean of 10 beats Calculations of derived indices were performed according to standard methods Coronary sinus blood flow was measured by the thermodilution method[3] and special care was taken to maintain the catheter in the same position in the coronary sinus throughout the entire length of the study Under these conditions variations between two successive measurements in our laboratory did not exceed 5 per cent

Statistical analysis was performed with the use of a paired t test for comparison of hemodynamic data within the same subjects

Results

Hemodynamic and metabolic effects of diazepam Table II summarizes the data on the hemodynamic and metabolic effects of diazepam

and altered autonomic tone due to pain and anxiety These preliminary results suggest that intravenous diazepam may be the sedative agent of choice in these patients Diazepam may also have a place in addition to conventional therapy in the management of patients with severe low output left heart failure In patients with complications of acute myocardial infarction such as hypotension and pulmonary edema some caution should be exercised since diazepam could further aggravate the hypotension and the derangement in blood gas equilibrium

Summary

Diazepam (0 1 mg per kilogram) was given intravenously to 12 patients with hemodynamic left ventricular failure at the time of cardiac catheterization Anxiety was effectively relieved in 10 patients Systemic and coronary hemodynamic parameters were assessed before and 5 and 15 minutes after diazepam Heart rate cardiac index and left ventricular stroke work index did not change significantly Mean aortic pressure decreased in all patients (average of 10 mm Hg) and left ventricular end diastolic pressure (LVEDP) decreased from a mean $\pm$ S E M of 24 3 $\pm$ 3 mm Hg at rest to 16 $\pm$ 2 1 at 5 minutes ($p < 0\,001$) and 15 8 $\pm$ 2 1 at 15 *minutes* ($p < 0\,002$) Left ventricular angiography performed 30 minutes after diazepam did not increase LVEDP above the pre diazepam control value Systolic ejection period and tension time index also decreased significantly after diazepam Coronary hemodynamics and myocardial metabolism were unaltered by diazepam The fall in *LVEDP induced by diazepam* is probably secondary to a decrease in arterial pressure (afterload) possibly associated with a decrease in *venous* return (preload) Our data therefore suggest that diazepam exerts a beneficial action on depressed left ventricular function and thus may be a sedative agent of choice in patients with myocardial infarction and heart failure

We thank Miss Diane Asselin Mr Roland Cardinal Mr A Gauthier and Mr C Guérard for their assistance in the preparation of this work.

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rest to 2,726 ± 232 at 5 minutes ($p < 0.002$) and 2,567 ± 222 at 15 minutes ($p < 0.001$)

Data on changes in coronary circulation and myocardial oxygen and lactate metabolism are presented in Table II Coronary sinus blood flow was unchanged after diazepam There was a slight but insignificant decrease in coronary vascular resistance and left ventricular oxygen consumption Myocardial oxygen and lactate extraction were unchanged after diazepam

Clinical and respiratory effects of diazepam Sedative effects were observed following drug administration in 10 of the 12 patients There was some variability in the degree of sedation Five patients became drowsy one patient complained of light headedness and dizziness and two patients had no clinical effects Ventilatory parameters and blood gas data are shown in Table III Ventilation decreased significantly 12 to 15 minutes after diazepam while respiratory rate was unchanged Thus hypoventilation was due primarily to a decrease in tidal volume Analysis of arterial blood gases at 5 minutes reflected the observed hypoventilation By 15 to 20 minutes after diazepam arterial Po_2, Pco_2 and pH had returned to near control levels

Discussion

In this study intravenous administration of diazepam to a group of patients with hemodynamic evidence of left ventricular failure and/or decreased left ventricular compliance produced a substantial fall in the left ventricular end diastolic pressure this effect persisted for at least 30 minutes Since our study was performed over a short period of time and was combined with a diagnostic investigation, it was not possible to determine the duration of the drug effect Of interest, however was the fact that following left ventriculography at the end of the 30 minute observation period the usual rise in left ventricular end diastolic pressure above control levels did not occur in our patients[6]

In a recent report,[7] we have shown that normal resting left ventricular end diastolic pressure was also decreased following administration of diazepam to patients with or without coronary artery disease Heart rate cardiac output and coronary sinus blood flow were within the normal range and remained unchanged in these patients, however mean arterial pressure and left ventricular oxygen consumption decreased significantly

Only a few other reports[4,5] have dealt with the hemodynamic effects of diazepam in man and the action of this drug on left ventricular end diastolic pressure has not been described Dalen and co workers[4] have reported a similar decrease in arterial blood pressure after intravenous diazepam in 15 patients with congenital and valvular heart disease studied under similar conditions Ten of their 15 patients had hemodynamic evidence of left heart failure at rest but post diazepam left ventricular end diastolic pressure was not reported in their study

In the present study this decrease in elevated left ventricular end diastolic pressure without any increase in heart rate left ventricular work and myocardial oxygen consumption appears to be beneficial Since heart rate coronary hemodynamics and myocardial metabolism were not modified by diazepam the fall in aortic pressure or decrease in afterload associated with a diminution in preload possibly through a reduced venous return, probably contributed to the observed diminution in left ventricular filling pressure

It has been demonstrated recently that drugs such as nitroglycerin[8] and nitroprusside[11] substantially improve left ventricular performance in patients with acute myocardial infarction and low output heart failure secondary to coronary artery disease or cardiomyopathy These agents primarily decrease the pressure load of the heart or aortic impedance and reduce left ventricular filling pressure and increase cardiac output without any change in heart rate or myocardial contractility

The results of the present study demonstrate that diazepam has a very similar action Although average cardiac output was normal and remained unchanged after diazepam in our patients, it may be expected that cardiac output would probably rise after diazepam in patients with low output cardiac failure Cardiac index was below 2.5 L/min/M^2 in all three patients with a functional Class III or IV in this study and increased after diazepam administration in two of the three patients It has been shown with both nitroglycerin[9] and nitroprusside[10] that cardiac output increases only in patients in whom it is depressed prior to administration of the drug

In patients suffering from an acute myocardial infarction the hemodynamic status is often complicated by depressed myocardial function

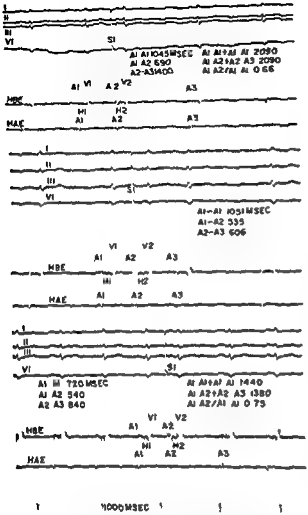

Fig 1 Improvement in sinus node function following atropine Top panel At a basic cycle length (A1 A1) of 1 045 msec a *premature atrial depolarization is introduced at a coupling* interval (A1 A2) of 690 msec The return test cycle length (A2 A3) is 1 400 msec The sum of the test and return cycle lengths (A1 A2 + A2 A3) is equal to the sum of two spontaneous sinus *cycle lengths (A1 A1 + A1 A1)* $\pm$ 5 msec indicating that the premature atrial depolarization occurring at [illegible] per cent of the sinus cycle has not penetrated and reset the sinus node Middle panel Subsequent introduction of premature atrial stimuli at 535 msec resulted in marked shortening of the return cycle (A2 A3) to a value less than the spontaneous sinus cycle The return atrial depolarization A3 exhibits a normal sequence of depolarization and appears to represent a sinus node echo Bottom panel Following atropine the sinus cycle length is reduced to 720 msec Introduction of premature atrial stimuli at 540 msec results in a return cycle (A2 A3) of 840 msec The sum of the test and return cycles is 1,380 msec This value is less than the sum of two spontaneous sinus cycles (1 440 msec) suggesting that the premature atrial impulse has penetrated and reset the sinus node Following atropine sinus node reset occurred at 75 per cent of the sinus cycle Sinus node echoes were no longer seen after atropine

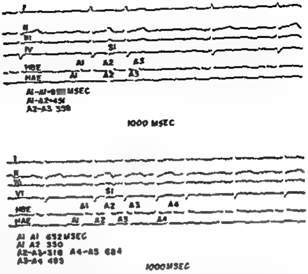

Fig 2 Top panel At a basic sinus cycle of 9[illegible] msec introduction of a premature atrial stimulus at a test cycle length (A1 A2) of 4[illegible]1 msec results in abrupt shortening of the return cycle length with an A1 A2 interval of 359 msec The sequence in depolarization from high to low right atrium and the presence of an upright P wave in Lead II is consistent with the appearance of a single sinus node echo Bottom panel Following atropine the basic sinus rate (A1 A1) is reduced to 652 msec No evidence of sinus node echoes appeared until a coupling interval (A1 A2) of 350 msec was reached At this test interval there is abrupt shortening of the return (A2 A3) cycle to 318 msec, followed by a second sinus node echo with an A3-A4 interval of 495 msec This sequence illustrates a shift in the coupling interval necessary to produce sinus node echoes and the addition of a second sinus node echo following atropine

beat the basic sinus cycle (A1 A1) the test cycle (A1 A2) and the interval between the test and return sinus cycle (A2 A3) are shown In addition the value for twice the sinus cycle (A1 A1 + A1 A1) and the interval obtained by adding the test atrial cycle and return atrial cycle (A1 A2 + A2 A3) are shown In beats 1 through [illegible] the sum of the test atrial cycle and return atrial cycle (A1 A2 + A2 A3) [illegible] equal to or greater than the sum of two spontaneous sinus cycles (A1 A1 + A1 A1) This finding suggests that beats 1 through 6 were not sensed by the sinus node and sinus reset did not occur so that the sinus pause was fully compensatory In beats 7 through 11 the sum of the test and return atrial cycles (A1 A2 + A2 A3) is less than the sum of two preceding sinus cycles (A1 A1 + A1 A1) by at least 30 msec This finding suggests that the premature atrial depolarization has penetrated and reset the sinus node so that the sinus node pause is less than compensatory

Improved sinus node sensing after atropine

Joe K Bissett, M D
Neil de Soyza M B B S
James J Kane, M D
Neil M Schmitt Ph D
Little Rock Ark

Recent studies have shown that sinoatrial function may be evaluated by premature atrial stimulation[1] Examination of the effect of premature atrial stimuli with variable coupling intervals on sinus node function has demonstrated two types of responses[1] Atrial stimuli occurring late in the sinus cycle do not appear to penetrate and reset the sinus node In this area (zone I) the sinus node pause is fully compensatory Premature atrial stimuli occurring earlier in the cardiac cycle may reset the sinus node pacemaker (zone II) and the sinus node pause is not fully compensatory[1,2] Demarcation of these zones of sinus node response may permit quantitation of the effects of drug intervention on sinus node sensing The *purpose of this study is to demonstrate alterations* in sinus node sensing produced by atropine The data also show changes in sinoatrial conduction time and provide examples of the response of sinus node echoes to atropine administration

Methods

After obtaining informed consent evaluation of sinus node function was performed in 10 patients (mean age 50 ± 5 years) undergoing diagnostic catheterization for evaluation and treatment of chest pain The patients were brought to the catheterization laboratory in the nonsedated postabsorptive state and His bundle electrograms were obtained by the introduction of a bipolar catheter percutaneously into the right femoral vein A quadripolar catheter was introduced into the superior portion of the right atrium for recording of the atrial electrogram and atrial pacing Simultaneous recording of Leads I, II, III and V_1 (Figs 1 and 2) were obtained on a multichanneled oscilloscope recorder (Electronics for Medicine)

With the use of an SR digital pacemaker premature atrial stimuli 2 msec in duration at twice the diastolic threshold were introduced through a stimulus isolation box (Tektronix) after every tenth sinus beat Premature atrial stimuli were moved in 20 msec increments so that the entire atrial diastolic cycle was scanned[1] *During introduction of premature atrial stimuli* the following measurements were obtained (1) the interval between the last preceding sinus P waves (A1 A1) (2) the interval between the last sinus P wave and atrial premature depolarization or test atrial stimulus (A1 A2) and (3) the return cycle (A2 A3) or interval between the test atrial stimulus and the next spontaneous atrial beat

With these data the following calculations were done (1) the interval between the last sinus and premature atrial stimulus (A1 A2) at which reset of the sinus pacemaker occurred in all subsequent premature atrial stimuli introduced at shorter cycle lengths and (2) sinoatrial conduction time calculated by the method of Reiffel and associates[3]

The conduction interval representing the demarcation between reset and nonreset of the sinus node was calculated as shown in Table I In this table the response of the sinus node to the introduction of premature atrial stimuli in the midportion of the sinus cycle is shown For reference the beats are labeled 1 through 11 For each

From the Veterans Administration Hospital Department of Medicine and University of Arkansas School of Medicine Little Rock Ark

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Reprint requests Joe K Bissett M D Department of Medicine Veterans Administration Hospital 300 E Roosevelt Rd Little Rock Ark 72206

The sinoatrial conduction time was then calculated as half the value of the mean return test atrial cycles (A2 A3) during the period of sinus node reset minus the mean of all sinus cycles (A1 A1) during this period[1]

In each of the 10 patients evaluation of sinus node function was completed before and 5 to 10 minutes after the administration of atropine in doses ranging from 0 5 to 1 0 mg In each case the atropine dose was sufficient to shorten the sinus cycle length by at least 150 msec (Table II)

Results

The results are shown in Table II and Figs 1 and 2 The mean sinus cycle length (A1 A1) was reduced from 909 ± 118 (S D) to 642 ± 75 msec Atropine administration produced a significant alteration in the portion of the sinus cycle during which the sinus node was reset by premature atrial stimuli (Fig 1 and Table II) Before atropine premature atrial stimuli induced reset of the sinus node at 71 ± 8 per cent of the sinus cycle Following atropine later premature atrial stimuli were sensed and reset the sinus node as shown by a mean value for the area of sinus node reset of 83 ± 5 per cent ($P < 0.01$) In each of the cases studied atropine induced not only a shortening of the sinus cycle but an increase in the percentage of the cycle during which sinus node reset occurred (Table II)

The sinoatrial conduction time was found to decrease in all patients studied (Table II) The mean sinoatrial conduction time evaluated before atropine was 109 ± 29 msec The mean sinoatrial conduction time obtained following atropine administration was 62 ± 23 msec ($P < 0.01$)

Abrupt shortening of the return cycle length (A2 A3) with early premature atrial stimuli was observed in two patients The effect of atropine on reset of the sinus node and the occurrence of abrupt shortening of A2 A3 consistent with sinus node echoes is illustrated in Fig 1 In this patient introduction of premature atrial stimuli as late as 66 per cent of the sinus cycle (top panel) was not associated with sinus node reset which occurred at 64 per cent of the sinus cycle Further introduction of atrial stimuli at a test cycle length of 540 to 500 msec was associated with an abrupt decrease in the length of the return cycle with a normal sequence of atrial depolarization suggesting the occurrence of sinus node echoes (middle panel) Following atropine the sinus cycle length was shortened as shown in the bottom panel of Fig 1 Introduction of premature atrial stimuli at a test cycle length of 540 msec produced penetration and reset of the sinus node pacemaker at value of 75 per cent of the sinus cycle length In addition the test stimulus was not observed to produce sinus node echoes after atropine The results of atropine on the occurrence of sinus node echoes is illustrated in a second case in Fig 2 In the top panel at a basic sinus cycle length of 952 msec introduction of a test atrial stimulus at 451 msec results in a short return cycle length of 359 msec Only single sinus node echoes were observed prior to atropine In the bottom panel the results following atropine are shown The basic sinus cycle length has been decreased to 652 msec and the zone of production of sinus node echoes has been reduced to 350 msec The return sinus cycle length of 318 msec is shorter than the basic sinus cycle length It is followed by a third atrial depolarization A4 which occurs at a shortened return cycle length of 495 msec Depolarizations A3 and A4 are associated with a normal sequence of high and low atrial depolarizations and upright P wave in Lead II, suggesting sinus node echoes This figure illustrates a shift in the coupling interval necessary to produce sinus node echoes and the addition of a second sinus node echo following atropine administration

Discussion

The results of this study show that the percentage of the sinus cycle length at which sinus node reset occurs is lengthened by atropine administration The anatomic correlation of this observation is unclear Anatomic and electrophysiologic studies have demonstrated that the sinoatrial node is composed of several interspaced groups of cells (P cells)[8] During conditions of varying autonomic tone the site of the sinus node pacemaker may shift within the sinus node so that the pathway of sinus node conduction may be altered[9] Alterations in the pathways of sinus node conduction with atropine administration may be responsible for the changes in sinus node sensing observed in this study

In each case studied the sinoatrial conduction time was observed to decrease following atropine These changes may again be due to alteration of sinus node pathways with changes in the autonomic tone The atropine induced reduction

Table I Measurement of the zone of sinus node reset

No	Zone I Nonreset (beats 1 6)						Zone II Sinus node reset (beats 7 11)				
	1	2	3	4	5	6	7	8	9	10	11
A1 A1	880	880	810	860	850	840	860	880	880	840	880
A1 A2	780	760	740	720	700	680	660	640	620	600	580
A2 A3	980	1 000	980	1 000	1 000	1 000	1 000	1 020	980	1 000	1 000
A1 A2 + A2 A3	1 760	1 760	1 720	1 730	1 700	1 680	1 660	1 660	1 600	1 600	1 580
A1 A1 + A1 A1	1 760	1 760	1 680	1 720	1 700	1 680	1 720	1 760	1 760	1 680	1 760
Comment	Nonreset	Nonreset	Nonreset	Nonreset	Nonreset	Nonreset	Reset	Reset	Reset	Reset	Reset

Table II Results of conduction studies

Patient	Before atropine				After atropine			
	Mean sinus cycle length	A1 A2 interval at onset of sinus node reset	Per cent sinus cycle at onset of reset	Sinoatrial conduction time	Mean sinus cycle length	A1 A2 interval at onset of sinus node reset	Per cent sinus cycle at onset of reset	Sinoatrial conduction time
1	860	670	0.78	70	560	470	0.84	41
2	810	450	0.56	170	590	460	0.78	81
3	1 070	680	0.64	104	700	550	0.78	70
4	1 020	840	0.84	72	690	650	0.88	44
5	760	490	0.64	122	590	470	0.80	72
6	820	470	0.69	130	640	550	0.86	28
7	820	630	0.77	104	620	530	0.85	47
8	850	590	0.69	99	640	580	0.91	50
9	1 070	740	0.69	115	825	630	0.76	87
10	1 000	780	0.78	100	630	520	0.83	95
	909 ± 118	644 ± 124	0.71 ± 0.08	109 ± 29	642 ± 75	531 ± 54	0.83 ± 0.05	62 ± 21

$P < 0.01$ when compared with control value

In several cases isolated beats might be sensed as the demarcation zone between nonreset and reset of the sinus node was approached In each patient however a point was reached at which all subsequent premature atrial stimuli introduced at shorter coupling intervals penetrated and reset the sinus node, even in the presence of sinus arrhythmia This point was taken as the interval between nonreset and reset of the sinus node In the example shown this value occurred at a test cycle length between 660 and 680 msec and was recorded as 670 msec In each case the test cycle length at which all subsequent premature atrial stimuli reset the sinus node was expressed as a percentage of the mean basic cycle length (Table II)

The sinoatrial conduction time was estimated by examining the response of the sinus node during the period in which the sinus node was penetrated and reset by premature atrial stimuli During this zone the value of the return cycle (A2 A3) was taken as an approximation of the duration of conduction from the premature atrial contraction into the sinus node plus the time required for the next sinus node depolarization to occur (A1 A1) plus the time necessary for conduction of the impulse out of the sinus node to the atrium where the next atrial depolarization occurred and was recorded As previously reported the return cycle length A2 A3 then equals the basic sinus cycle A1 A1 plus the conduction time into and out of the sinus node [1]

The sinoatrial conduction time was then calculated as half the value of the mean return test atrial cycles (A2 A3) during the period of sinus node reset minus the mean of all sinus cycles (A1 A1) during this period

In each of the 10 patients evaluation of sinus node function was completed before and 5 to 10 minutes after the administration of atropine in doses ranging from 0 5 to 1 0 mg In each case the atropine dose was sufficient to shorten the sinus cycle length by at least 150 msec (Table II)

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In each case studied the sinoatrial conduction time was observed to decrease following atropine These changes may again be due to alteration of sinus node pathways with changes in the autonomic tone The atropine induced reduction

of sinoatrial conduction time is consistent with a recent report showing shortening of sinoatrial conduction time following administration of atropine and isoproterenol [10] These changes may be opposite in direction to changes produced by spontaneous variations of the sinus cycle length during normal sinus depolarization [1]

In two patients atropine was observed to effect the onset of sinus node echoes In one case atropine was observed to abolish sinus node echoes This phenomenon may have occurred because improvement in sinus node function eliminated conditions necessary for sinus node re entry In a second case atropine was observed to shift the test coupling interval necessary for the production of sinus node echoes Similar findings have been reported in a recent study [4] suggesting that alterations in sinus node function may have beneficial as well as detrimental effects on the occurrence of sinus node echoes in man Further study of the production of sinus node echoes with graded doses of atropine may permit further understanding of this phenomenon

The results of this study demonstrate improved sinus node sensing following atropine Reduction of vagal tone appears to allow earlier recognition of premature atrial stimuli which then penetrate and reset the sinus node Understanding of this effect may facilitate interpretation of the complex electrophysiologic effects of atropine on the human conduction system

Summary

Although atropine is known to increase sinus rate through its vagolytic effect, the effects of atropine on sinus node sensing are unknown The purpose of this study was to investigate alterations in sinus node sensing produced by atropine Measurement of the zone of sinus node reset and sinoatrial conduction time was performed in 10 patients by programmed premature atrial stimulation The zone of sinus node reset was determined as the transition point where premature atrial stimuli were followed by a less than compensatory pause Sinoatrial conduction time was calculated from sinus node return cycles in the area where sinus node reset occurred

Atropine administration produced a significant increase in the percentage of the sinus cycle length at which premature atrial contractions penetrated and reset the sinus node Sinus node reset occurred at a mean percentage of the sinus cycle of 71 ± 8 per cent before atropine and 83 ± 5 per cent after atropine ($P < 0.01$) The sinoatrial conduction time was significantly reduced from 109 ± 29 to 62 ± 23 msec ($P < 0.01$) after atropine as sinus cycle length was reduced from 909 ± 118 to 642 ± 75 msec after atropine Sinus node echoes were observed in two patients In one patient atropine abolished the appearance of sinus node echoes In the second patient atropine reduced the coupling interval necessary to produce sinus node echoes but appeared to facilitate sinus node re entry by the appearance of an additional sinus node echo and a reduction in the echo cycle length

This study demonstrates that atropine produces significant improvement of sinus node sensing in man

The authors gratefully acknowledge the secretarial assistance of Miss Lisa Goodwin

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Residual effects when chronic propranolol therapy is discontinued within 48 hours of cardiopulmonary bypass

G Frank O Tyers M D F R C S (C) F A C S
Howard C Hughes Jr V M D
Hershey Pa.

The consequences of administering propranolol a competitive beta adrenergic blocking agent include decreases in the following parameters myocardial contractility automaticity and oxygen consumption heart rate cardiac output coronary blood flow renal blood flow urinary sodium excretion plasma volume catecholamine induced glycogenolysis in muscle and free fatty acid release from adipose tissue Coronary vascular resistance atrioventricular conduction time systolic ejection period ventricular volume and airway resistance are increased [illegible] Propranolol s effects on blood pressure and systemic resistance are variable depending upon route of administration level of endogenous catecholamines (pressor effects enhanced) and concurrently administered agents

After chronic propranolol therapy has been discontinued the duration of continuing hemodynamic effects and the safety and optimal timing of cardiopulmonary bypass for aortocoronary surgery are in dispute [illegible] The present study was undertaken to determine if drug related hemodynamic alterations persisted when cardiopulmonary bypass was undertaken 8 and 48 hours after chronic oral propranolol administration had been discontinued

Methods

Three groups of mongrel dogs weighing 15 to 18 kilograms were prepared for cardiopulmonary bypass The first group of six animals received no drugs prior to surgery and served as a control Twelve dogs were given 40 mg of propranolol orally twice daily for 3 to 5 weeks Six of these animals were operated upon approximately 8 hours after the last oral dose of propranolol had been administered and six had surgery initiated 49 hours after the last oral dose of propranolol All animals were fasted overnight anesthetized with sodium pentobarbital (30 mg per kilogram) intubated and maintained on positive pressure ventilation Arterial blood gases were determined frequently throughout the study Appropriate adjustments were made in the respirator oxygen concentration and sodium bicarbonate administration to maintain a pH of 7 4 ± 0 05 a base excess of 0 ± 2 a Po_2 of 100 ± 20 mm Hg and a Pco_2 of 40 ± 5 mm Hg The femoral artery and right atrium via the femoral vein were cannulated for pressure measurements Following median sternotomy intravenous heparin was administered (3 mg per kilogram) and the aorta superior vena cava and inferior vena cava were cannulated for bypass A short rigid plastic cannula was passed into the apex of the left ventricle and attached to a Statham pressure transducer sutured to the abdomen at the lower end of the sternotomy incision A Lead II electrocardiogram (ECG) and all pressures were recorded during the study with a DR 12 Electronics for Medicine recorder Prior to bypass, cardiac output left ventricular end diastolic pressure peak systolic pressure and heart rate were measured at central venous pressures of 5 10 and 15 mm Hg Cardiac output measurements were computed in the standard manner by means of the dye-dilution technique with indocyanine green All animals were

From the Departments of Surgery and Comparative Medicine The College of Medicine The Milton S Hershey Medical Center of The Pennsylvania State University Hershey Pa

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Reprint requests G Frank O Tyers, M D Department of Surgery College of Medicine The Milton S Hershey Medical Center Hershey Pa 17033

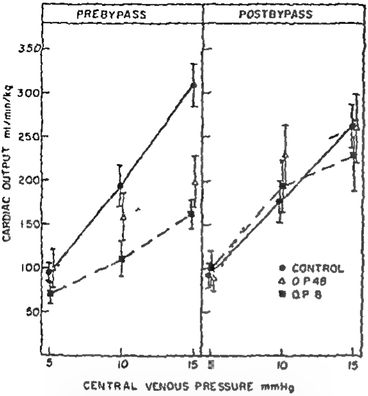

Fig 1 Cardiac outputs prior to and following cardiopulmonary bypass in the control group and in dogs that had received oral propranolol until 8 hours (O P 8) and 48 hours (O P 48) prior to surgery

then placed on total cardiopulmonary bypass with the use of a Sarns modular pump and a disposable Bentley pediatric bubble oxygenator with integral heat exchanger The heart was not arrested After 1 hour total cardiopulmonary bypass was discontinued and the animals were allowed to recover for 30 minutes Cardiac function determinations were repeated at the same preloads No drug support was used or required in any of the animals in the study Left ventricular samples were taken for histopathologic study immediately following completion of the post bypass physiologic studies The tissues were fixed in 10 per cent neutral buffered formalin sectioned at 5 μ and stained with hematoxylin and eosin phosphotungstic acid hematoxylin and Lie s hematoxylin–basic fuchsin–picric acid Systemic resistance was calculated in dynes sec/cm^{5} using the formula $R = \Delta P \times 1333/Q$ where R equals the resistance, ΔP equals the mean systemic pressure less the right atrial pressure (in mm Hg) and Q equals the cardiac output (in ml/sec) Student s t test was used for comparison between groups and the paired t test for comparisons of pre and postbypass values in the same animals

Results

The oral administration of propranolol resulted in a mean decrease in heart rate from 195 8 ± 2 0 to 95 3 ± 5 3 ($p < 0.001$) a transient increase in P R interval, and a persistent prolongation of the Q T interval (Table I) All control and experimental animals tolerated surgery, prebypass studies, cardiopulmonary bypass and postbypass studies without difficulty

Hemodynamic studies

Prior to bypass there were no significant differences in cardiac output when the three groups were compared at a central venous pressure of 5 mm Hg (Fig 1) However, at a central venous pressure of 10 mm Hg the mean cardiac output was reduced in both the groups that had been receiving propranolol and this reduction was significant ($P < 0.02$) in the animals that had received their last oral dose of propranolol approximately 8 hours prior to surgery When the central venous pressure was increased to 15 mm Hg the cardiac function curves further separated Control animals increased their cardiac outputs 200 per cent as compared with their cardiac outputs at a central venous pressure of 5 mm Hg whereas the animals that had received their last oral dose of propranolol 48 hours prior to surgery increased their cardiac outputs only 100 per cent ($p < 0.05$) and the group that had received propranolol until 8 hours prior to surgery increased their cardiac outputs only approximately 50 per cent ($p < 0.01$) Thirty minutes following bypass there were no significant differences at any of the filling pressures studied when the cardiac outputs of the control and two experimental groups were compared (Fig 1) There were no significant differences between pre and post bypass cardiac output curves in the control group, although postoperative mean cardiac outputs were slightly reduced at each central venous pressure (Fig 2) In contrast, postcardiopulmonary bypass cardiac outputs were increased at central venous pressures of 10 and 15 mm Hg in both groups of animals that had received propranolol and these increases were significant at a central venous pressure of 10 mm Hg ($p < 0.05$) in the group that had received their last oral dose of propranolol 48 hours prior to surgery and at central venous pressures of 10 ($p < 0.02$) and 15 mm Hg ($p < 0.05$) in the group

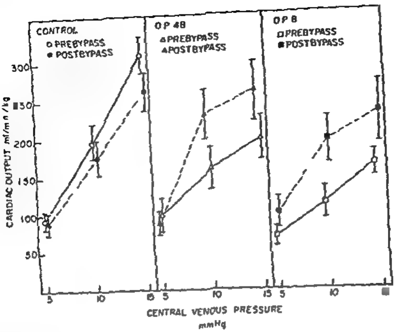

Fig 2 A comparison of the effects of cardiopulmonary bypass on the cardiac output in control and propranolol treated animals (abbreviations as in Fig 1)

Table I ECG Effects of chronic propranolol therapy (values ± S E)

Interval	Prior to treatment (sec)	After propranolol therapy (wk) 1 (sec)	2 (sec)	3 (sec)	4 (sec)	5 (sec)
P R	0 09 ± 0 002	0 10 ± 0 005	0 11 ± 0 004	0 10 ± 0 014	0 10 ± 0 010	0 10 ± 0 015
Q T	0 18 ± 0 004	0 2? ± 0 011	0 ?0 ± 0 004	0 21 ± 0 003	0.21 ± 0 007	0.22 ± 0 009

Significantly different paired t test $p < 0.01$ $p < 0.001$

that had received their last dose of propranolol 8 hours prior to surgery

When compared with control levels prior to bypass at central venous pressures of 10 and 15 mm Hg left ventricular end diastolic pressure was modestly elevated in both groups that had received propranolol but after bypass there were no differences among the three groups of animals (Fig 3) When pre and postbypass left ventricular end diastolic pressures were compared in the control and the study groups (Fig 4) there were no differences in the controls but at the higher filling pressures in the animals that had been receiving propranolol postbypass left ventricular end diastolic pressure was lower than prebypass left ventricular end diastolic pressure and this postbypass reduction was significant at a central venous pressure of 15 mm. Hg in the group that had been off propranolol for 48 hours prior to surgery ($p < 0.01$)

When compared with control levels prior to bypass at a central venous pressure of 15 mm Hg peak systolic pressures were significantly elevated ($p < 0.05$) in both groups that had received propranolol (Fig 5) Postbypass peak systolic pressures in the group that had received propranolol until 8 hours prior to surgery were elevated over control levels at central venous pressures of 5 ($p < 0.05$) 10 ($p < 0.02$) and 15 mm Hg ($p < 0.02$) Postbypass peak systolic pressures in the 8 hour group were also elevated at central venous pressures of 10 and 15 mm Hg ($p < 0.05$) over those in the group of dogs that had received propranolol until 48 hours prior to surgery (Fig 5) When pre and postbypass peak systolic pressures in each group were compared there were no

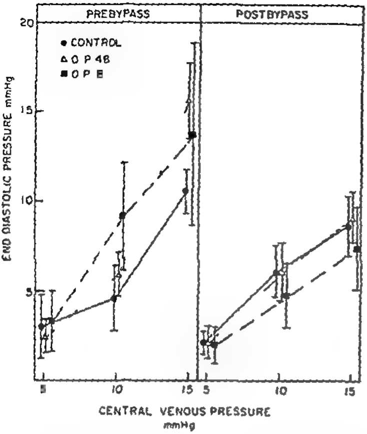

Fig 3 End diastolic pressure prior to and following cardiopulmonary bypass in the control group and in dogs that had received oral propranolol until 8 hours (*O P 8*) and 48 hours (*O P 48*) prior to surgery

significant differences in the control or either of the experimental groups at any central venous pressure (Fig 6)

The marked elevation of systemic resistance over control levels prior to cardiopulmonary bypass in the dogs that received propranolol until 8 hours prior to surgery is shown in Fig 7 ($p < 0.04$ at a central venous pressure of 5 mm Hg and $p < 0.02$ at a central venous pressure of 15 mm Hg) In the animals that received their last dose of propranolol 48 hours prior to surgery systemic resistance was only slightly elevated over control levels at a central venous pressure of 5 mm Hg but at central venous pressures of 10 mm Hg ($p < 0.01$) and 15 mm Hg ($p < 0.02$), systemic resistance was significantly elevated over controls Postbypass at all central venous pressures systemic resistance had fallen to only slightly greater than control levels in the group that received their last oral dose of propranolol 48 hours prior to surgery (Fig 7) but systemic resistance continued to be markedly elevated over control levels in the dogs that received their last oral dose of propranolol 8 hours prior to surgery ($P < 0.05$) When pre and postbypass levels of systemic resistance were compared in the three study groups there were no significant differences either in the control group where resistance remained low, or in the group that received their last dose of propranolol 8 hours prior to surgery where resistance remained high However, in the group that had propranolol discontinued 48 hours prior to surgery, systemic resistance fell during cardiopulmonary bypass and recovery (Fig 8) and this reduction was significant at a central venous pressure of 15 mm Hg ($P < 0.04$)

There were no significant differences in heart rate among the three groups studied either prior to or following cardiopulmonary bypass (Fig 9) although the mean heart rate in the group that received propranolol 8 hours prior to surgery was a little faster than the rate of either the control or other experimental group When pre and postbypass rates were compared in each group (Fig 10) there were no differences except in the group that received propranolol 8 hours prior to surgery where at a central venous pressure of 5 mm Hg the postbypass rate was slightly increased over the prebypass rate

Histopathologic studies

There were no significant differences between control and experimental animals Minor histologic changes attributable to cardiopulmonary bypass were present in all groups and consisted of small foci of degeneration and ischemia as evidenced by slight scattered staining with Lie's hematoxylin–basic fuchsin–picric acid The phosphotungstic acid–hematoxylin stain revealed no evidence of microemboli or thrombi

Discussion

Previous reports have indicated that cardiopulmonary bypass for coronary artery surgery may be safely undertaken within 24 hours of discontinuing chronic propranolol therapy 48 hours after chronic propranolol therapy had been discontinued [2] or only after propranolol had been discontinued for 2 weeks [4] The effects of propranolol therapy are complex and variable depending upon the isomer studied [4] individual metabolic variability [2,4] the duration of administration [?] and route of administration [?] While other active degradation products may occur, 4 hydroxypropranolol is of interest because it is present in the plasma only after oral administration of propranolol [4] This may explain the usual lack of a hypotensive effect when propranolol is administered parenterally [3] and the lack of persis

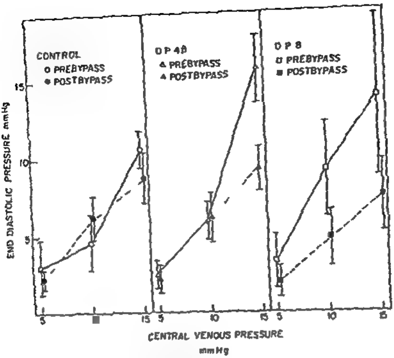

Fig 4 A comparison of the effects of cardiopulmonary bypass on the end-diastolic pressure in control and propranolol treated animals (abbreviations same as in Fig. 3)

tent effects after propranolol was withdrawn in the animal studies of Faulkner and associates[2] An additional criticism of clinical studies of continued hemodynamic effects after propranolol is withdrawn is their heavy reliance upon the return of the heart rate to normal or the normal response of the heart rate to isoproterenol Viljoen and associates referred to unpublished data which suggested that following withdrawal of propranolol therapy negative inotropic effects persist much longer than negative chronotropic effects The present study strongly supports this impression as heart rate had returned to normal levels by 8 to 10 hours after the last dose of propranolol whereas cardiac function especially in response to volume loading continued to be depressed prior to cardiopulmonary bypass 48 hours after the last oral dose of propranolol Cardiac output was decreased while left ventricular end diastolic pressure peak systolic pressure and systemic resistance were increased The magnitude of these differences was directly related to the central venous pressure and inversely related to the interval between the last dose of the drug and the measurements of cardiac function The marked reduction in heart rate during the chronic oral administration of propranolol due to suppressed sinoatrial node automaticity was the most evanescent of its effects

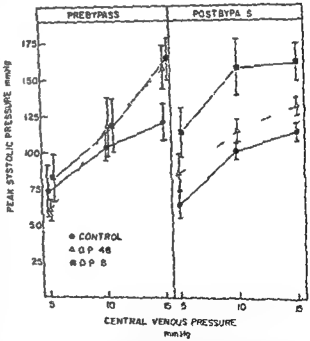

Fig 5 Peak systolic pressures prior to and following cardiopulmonary bypass in the control group and in dogs that had received oral propranolol until 8 hours (*O P 8*) and 48 hours (*O P 48*) prior to surgery

Atrioventricular conduction as measured by the P R interval, was not significantly prolonged after the first 2 weeks of oral administration but ventricular repolarization as measured by the Q

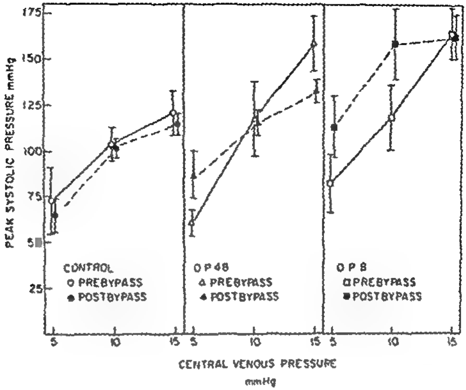

Fig 6 A comparison of the effects of cardiopulmonary bypass on the peak systolic pressure in control and propranolol treated animals (abbreviations same as in Fig 5)

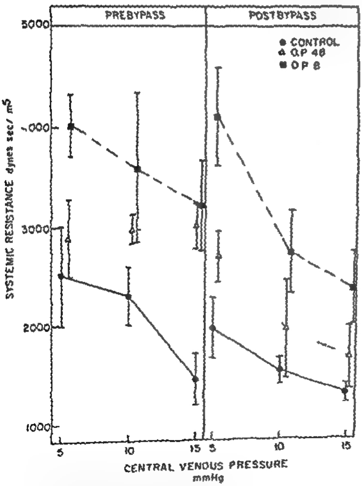

Fig 7 Systemic resistance prior to and following cardiopulmonary bypass in the control group and in dogs that had received oral propranolol until 8 hours (O P 8) and 48 hours (O P 48) prior to surgery

T interval, was significantly prolonged during chronic oral propranolol therapy

Following cardiopulmonary bypass cardiac output and left ventricular end diastolic pressures were within normal limits but peak systolic pressure and systemic resistance were still elevated over control levels, and these functional abnormalities were of real significance when the oral administration of propranolol was not stopped until the day prior to surgery

The time course of the persisting effects of drug therapy in this experimental study are in general agreement with our clinical experience in three patients who received chronic oral propranolol (lowest dose 40 mg daily) until between 8 and 36 hours prior to cardiopulmonary bypass surgery because of intractable angina or arrhythmia Low cardiac output and marked hypotension were encountered in each patient during the induction of anesthesia or early in the course of surgery and massive intravenous doses of epinephrine were required prior to and following aortocoronary bypass surgery Although the number of patients receiving chronic oral propranolol was small their course is in sharp contrast to our recent experience in over 300 other aortocoronary bypass patients where the 30 day operative risk is now 1 per cent including patients with unstable angina, recurrent angina following myocardial

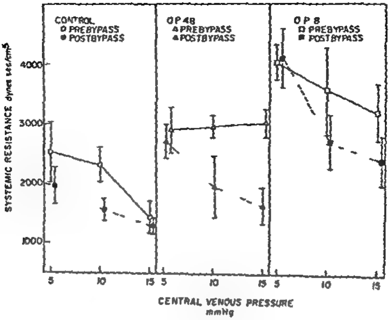

Fig 8 A comparison of the effects of cardiopulmonary bypass on the systemic resistance in control and propranolol treated animals (abbreviations same as in Fig 7)

infarction and all emergencies Between 48 and 60 hours after propranolol had been discontinued epinephrine dependence rapidly and unexpectedly diminished in the propranolol cases and the remainder of the postoperative course was unremarkable

The improvement in cardiac function following cardiopulmonary bypass in both the clinical and experimental experience may be due to the effects of time and the metabolic degradation of propranolol and its hemodynamically active breakdown products A dilutional and/or wash out effect upon propranolol and its metabolites cannot be ruled out however because postcardiopulmonary bypass cardiac output with volume loading was better in animals that had been off propranolol only 8 hours than prebypass levels in animals that had been off propranolol for 48 hours It would therefore appear that the deleterious effects of propranolol might be more pronounced after short periods of cardiopulmonary bypass or operations in which cardiopulmonary bypass was not used and this impression is supported by the results of internal mammary artery implantation in patients recently on propranolol When postbypass cardiac dysfunction is encountered in a patient who received chronic propranolol therapy to within 48 hours of surgery a prolonged period of partial (intra aortic balloon) or complete support is indicated since 40

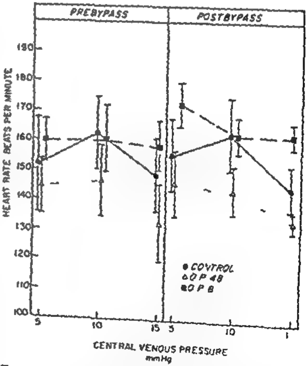

Fig 9 Heart rate prior to and following cardiopulmonary bypass in the control group and in dogs that had received oral propranolol until 8 hours (O P 8) and 48 hours (O.P 48) prior to surgery

to 60 hours following the last dose of propranolol the patient s condition may improve dramatically

In contrast to the similarity between the time

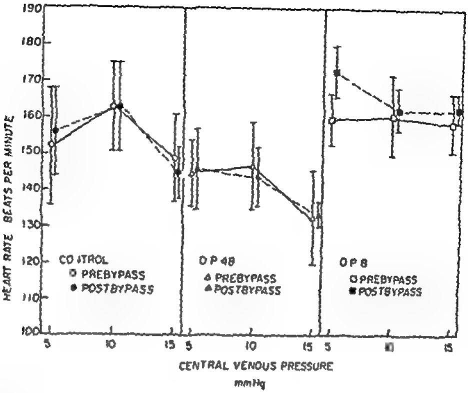

Fig 10 A comparison of the effects of cardiopulmonary bypass on the heart rate in control and propranolol treated animals (abbreviations same as in Fig 9)

course of the persistent effects of propranolol in the clinical cases and the experimental study cardiac function is often much more severely diminished in the clinical setting This difference is in part related to the combined deleterious effects of the propranolol and the ischemic heart disease Prognostically one must separate those patients left on propranolol without particular indication from those in whom the drug could not be discontinued because of severe symptoms Propranolol dependence while in hospital must often indicate severe diffuse ischemic myocardial disease A propranolol weakened ischemic myocardium receiving decreased coronary flow pumping against an increased peripheral resistance and responding poorly to volume loading can have little reserve with which to respond to the stresses of anesthesia and surgery

Is there an alternative to preoperative propranolol withdrawal in a patient with crescendo angina or severe rest pain requiring morphine while on full therapeutic doses of propranolol? There is almost certainly some risk in early surgery while drug effects persist but infarction can follow the withdrawal of propranolol in preparation for surgery Recently, three patients with persistent angina and/or ventricular tachyarrhythmias while receiving high dose propranolol therapy were stabilized prior to and during aortocoronary surgery by intra aortic counterpulsation In spite of a number of high risk factors (diabetes hypertension, recent myocardial infarction, systolic ejection fraction less than 0 30) all had benign intra and postoperative courses We currently recommend counterpulsation for all patients who continue to be symptomatic while on propranolol therapy for ischemic heart disease and for all patients who develop symptoms when propranolol therapy is reduced or withdrawn prior to surgery Preparation can then be made for semielective surgery with a minimum risk of preoperative myocardial infarction or serious arrhythmia and reasonable assurance of a stable intra and postoperative course

Summary

Recommendations regarding the safe waiting period between discontinuing chronic oral propranolol therapy and beginning cardiopulmonary bypass have varied from a few hours to 2 weeks In the present study utilizing adult dogs propranolol was discontinued 8 or 48 hours prior to surgery A reduction in cardiac output and elevations of left ventricular end diastolic pressure peak systolic pressure and systemic resistance were noted when cardiac function was evaluated

following the induction of anesthesia and prior to undertaking cardiopulmonary bypass The magnitude of these differences was directly related to the degree of volume loading and inversely related to the interval between the last dose of propranol and the determination of cardiac function Reduction of heart rate was the most evanescent of propranolol s hemodynamic effects as the marked bradycardia which persisted throughout the course of propranolol therapy was no longer evident 8 hours after the last oral dose of the drug.

Following total cardiopulmonary bypass of 1 hour s duration undertaken 8 hours after the last oral dose of propranolol cardiac output and left ventricular end diastolic pressure had returned to normal but peak systolic pressure and systemic resistance remained significantly elevated When 48 hours had elapsed between discontinuing propranolol and beginning cardiopulmonary bypass postbypass cardiac function was essentially normal with only slight persistent elevations of peak systolic pressure and systemic resistance detected

When the combined effects of ischemic heart disease and propranolol therapy the altered metabolic and hemodynamic effects of different routes of drug administration and the varying durations of cardiopulmonary bypass are taken into consideration some of the discrepancies between previously reported clinical and experimental findings regarding the duration of persistent propranolol effects can be understood The clinical course is usually benign in patients who have received propranolol to within a few hours of surgery without specific indication However it is often complicated when the drug is continued until just prior to surgery in patients dependant on propranolol for pain or arrhythmia control In patients demonstrating propranolol dependence control of symptoms with intra aortic balloon counterpulsation is recommended followed by the gradual withdrawal of propranolol and elective aortocoronary bypass surgery

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Changes in heart dipole moment after surgical correction of atrial septal defect

Clifford V Nelson
John T Dowling
Graeme Sloman
Portland Maine and Melbourne Australia

It is well known that right heart blood volume is abnormally high in the secundum type of atrial septal defect (ASD) There is also evidence that the left heart blood volume is lower than normal[1] Since intracardiac blood has a significant effect on the electrocardiogram (ECG) and these effects are modified by changes in cardiac blood volume[2] studies were made of changes in the ECG one or two weeks after surgical correction of ASD Such changes should be due to restoration of blood volume and possibly some regression of hypertrophy Preliminary experiments indicated that such changes do occur with a reversal of the VCG toward normal[3]

Methods

The vectorcardiogram (VCG) was measured a day or two before surgery with a lead system consisting of three rows of eight thorax leads plus a foot head lead[4] Potentiometers were used to adjust for thorax dimensions Voltages directly proportional to dipole moment components M_x M_y and M_z were recorded on three channels of magnetic tape These voltages were also applied to an analogue computer (EAI Model TR 22) patched to give spatial vector magnitude, M horizontal angle H° and vertical angle V° The axes and angles were in accordance with the recommendations of the A H A Committee on Electrocardiography[4] V° is the angle between M and the horizontal (transverse) plane positive values downward (inferior) range ±90° H° is the angle between the projection of M on the horizontal plane and the +X axis, positive values counterclockwise (posterior), range ±180° Positive x y and z axes are to the left down and posterior, respectively

The computer output voltages were also recorded on magnetic tape and a respiration signal was recorded on the seventh channel All VCG analyses were done at the expiratory phase of respiration The magnetic tape data were replayed at a lower speed on to a Honeywell 1507A Visicorder The VCG was repeated in most cases 7 to 14 days after surgical correction of the ASD

Patient population A total of 20 patients were studied of which four were male and 16 were female They were divided into two main groups as follows

Group A (eight patients) Secundum defects with normal pressures and no apparent pulmonary valvular stenosis (PVS) One patient (K B) had anomalous pulmonary venous drainage Six of this group had their defects repaired

Group B (seven patients) Secundum defects with right ventricular pressure greater than 30 mm Hg (range 33 to 64 mm Hg) Three of these had surgery One of this group (T T) also had anomalous pulmonary venous drainage

From the Department of Research Maine Medical Center Portland Maine and the Cardiac Department Royal Melbourne Hospital Melbourne Australia

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Reprint requests C V Nelson Ph D Maine Medical Center Portland Maine 04102

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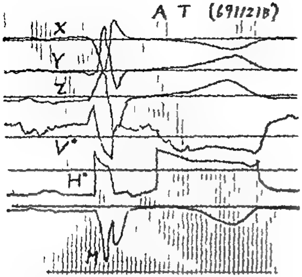


Fig 1 Visicorder record for a normal subject (A T) Positive deflections are downward except for the Y lead Th top three traces are directly proportional to M M and M Time lines at 10 msec intervals

One patient not included in the above groups had severe PVS with a right ventricular pressure of 100 mm Hg as well as a small secundum ASD There were also four patients with primum defects two of whom had their defects repaired Data from these five patients were treated separately

A total of 15 normal subjects (normals) were measured 14 of which were male The age range was 22 to 35 years except for one 11 year old boy

Results

Normal subjects An actual Visicorder record is shown in Fig 1 The values of M H° and V° during QRS for the same subject are shown in Fig 2 These curves are typical of all normals studied although there were minor variations The curves of M were more variable There were usually two distinct peaks but in some cases there was only one large peak and in a few cases there was also a small very early peak

In order to classify the peaks a table was first made of the directions of the peaks (Table I) Space was divided into eight sectors A vector pointing to the left posterior and downward for example is defined as pointing into sector 1 The sequence of resultant ventricular excitation can then be represented by a series of numbers The

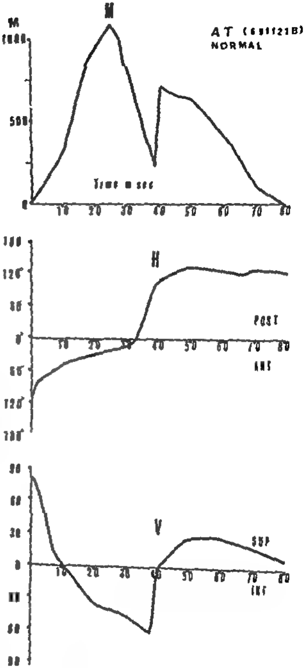


Fig 2 Spatial dipole moment M and angles during QRS for the same subject as in Fig 1 The units of M are in k mA -cm., where k is the average thorax conductivity

sequence of A T (Figs 1 and 2) was thus 84126

Next a table was made of the sectors corresponding to the peaks and the percentages of QRS duration (PQD) in which each peak occurred (Table II) This table is divided into 5 per cent intervals and the numbers in the table

Table I Definition of sector directions

Sector	M	M,	M	Direction	Symbol	H°	V°
1	+	+	+	Left posterior down	LPD	0° to 90°	0 to 90
2	−	+	+	Right posterior down	RPD	90 to 180	0 to 90
3	−	+	−	Right anterior down	RAD	−90 to −180	0 to 90
4	+	+	−	Left anterior down	LAD	0° to −90°	0° to 90
5	+	−	+	Left posterior up	LPU	0 to 90°	0 to −90°
6	−	−	+	Right posterior up	RPU	90 to 180°	0 to −90°
7	−	−	−	Right anterior up	RAU	−90 to −180	0° to −90
8	+	−	−	Left anterior up	LAU	0 to −90	0° to −90

Table II M peaks and sectors for normals

Subjects	Per cent of QRS duration																	Sequence
	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	
S W							4					6						78456
R M							4					6						34126
J C								1							6			7841262
A T									4					6				84126
J R			7						1									74126
P H									4						6			341262
P C				7*						1								784126
P V	M			7	M				1			M				8		74178
T D				7*						1								78412678
A B			7						1				2					741268
B H		4					4					6						784126383
F B									1				1					741514
J N			7					1				1						74121
S P		7							1				5					74158
L L									4					6				143115658

*Not a definite peak

refer to the sectors into which the peaks pointed In some cases there was not a real peak, but rather a bulge in the M curve which was repeated in successive complexes

On the basis of Table II it was possible to divide the peaks into three groups which we designate M_1, M_2, and M_3 All but one of the M_1 peaks, corresponding to septal and early RV excitation, were in sector 7 (RAU) The M_2 peaks corresponding to free wall excitation of the ventricles were either in sectors 1 or 4, i e to the left and downward and either somewhat posterior or anterior The M_3 peaks were mostly in sector 6 (RPU) corresponding to late excitation of basal parts of ventricle and septum The sequence of excitation for each subject is also shown in Table II The most common sequence was 74126 which corresponds to the classical pattern of cardiac excitation

In Table III, the first column gives mean values and standard errors of the means for the normals It is evident that M_2 was the largest peak with a mean ratio of M_2 to M_1 values of 2 37 The mean duration was 88 4 msec

Patients A table similar to Table II was made for all patients (not shown) In the normals there were 10 persons with two peaks and five with three peaks There were no individuals with more

Table III Mean values of dipole moment magnitude direction and times of occurrence of peaks for normals and patients

	Normals 1 Mean ± S E	All patients preoperative values 2 Group A	3 Group B	Surgical patients AO and PO values 4 Group A AO	5 Group A PO	6 Group B AO	7 Group B PO
M	04 ± 29	194	65	202	200	66	55
H	−100 ± 5	−99	−131	−96	−88	−131	−122
V	−16 ± 4	−18	−7	−16	−6	−7	9
t (msec)	14 5 ± 1 4	14 1	9 4	14 4	14.8	9 4	9 6
t (PQD)	16 3 ± 1 6	14 6	9 6	14 9	16 5	9 6	11 9
M	9 8 ± 7	504	310	489	664	217	289
H	−1 ± 5	−5	−16	−6	−23	−14	−24
V	40 ± 4	21	34	22	29	34	28
t_1(msec)	38 3 ± 1 3	34 4	3^7 4	33.9	33 2	28.9	27 0
t_1(PQD)	43 3 ± 1 2	35 9	32 5	35 2	38 5	30.3	33.3
$M_{..}$		359	478	290	405	354	304
H		−1^72	−94	−157	−138	−93	−86
$V_{..}$		23	4^9	3^7	26	47	54
t_1 (msec)		53.5	5^9 7	64.3	57 1	46 5	42.4
t_1 (PQD)		55 6	51 7	61.8	60 5	48 4	57 2
M	39_ ± [illegible]	328	396	339	396	359	369
H	98 ± 16	168	−145	169	174	176	−173
V	−10 ± 5	−15	2	−17	−21	1	6
t (msec)	58 9 ± 1 7	68 0	65 3	67 4	59 0	60 1	54.2
t_1(PQD)	64 0 ± 1 8	69 9	65 4	70 1	68.5	63 0	67.2
Duration (msec)	88 4 ± 1 3	93 8	101 0	96 0	85 8	96.9	81 0

Only patients who had M PO listed

than three peaks For the patients however the majority had three or four peaks The first early peak was designated M_1 The next was designated M_2 If there were two additional peaks these were designated M and M The times of occurrence and sector directions were helpful in making the classifications It [illegible] significant that most of the patients had an M_2 peak this did not occur in any of the normals

Columns 2 and 3 in Table III give mean preoperative values for all patients in Groups A and B Some of these did not have surgery Columns 4 to 7 give preoperative (AO = anteoperation) and postoperative (PO) data for the patients who had their ASD s repaired We did not think it advisable to give statistical data for the patients because of the limited numbers The mean values in Table III can be compared with the standard errors of the means for the normals In repeated samples from a large population 68 per cent of the means would fall within the range of ±1 standard error 95 per cent within ±2 S E and 99 7 per cent within ±3 S E If the mean value for the patient data differs by more than two or three standard errors from the normal mean it is probably a significant difference

Mean QRS durations are listed at the bottom of Table III It is seen that the durations for the patients were considerably longer than for the normals and that the durations decreased to normal 1 to [illegible] weeks after surgery Changes in times of the various peaks PO when expressed as a percentage of QRS duration were probably due partly to changes in QRS duration

Septal and early RV excitation M_1 Only four of the Group A and two of the Group B surgical patients had M_1 peaks For both normals and patients the M vector pointed to the right anterior and upward For Group B M_1 was much smaller than for the normals or Group A and

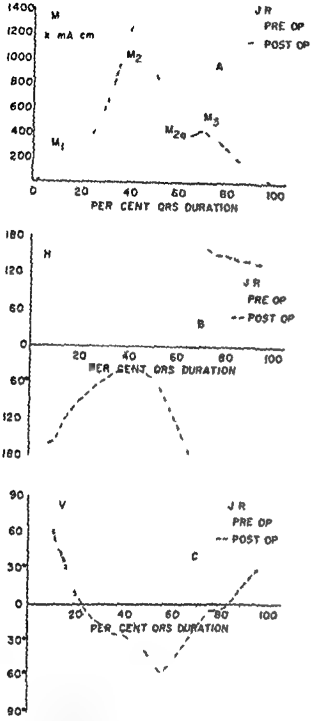


Fig 3 Curves of M H° and V for patient J R before and 12 days after surgical correction of secundum ASD This was a 19 year old female patient with normal RV and PA pressures The flow ratio was 3 8 The H° curve shows that the horizontal vector swings back to the anterior before going posterior (compare with Fig 2) The similarity in the AO and PO angles indicates that the changes in M were not caused by rotation of the heart The excitation sequence was 678132626 AO and 6784326 PO

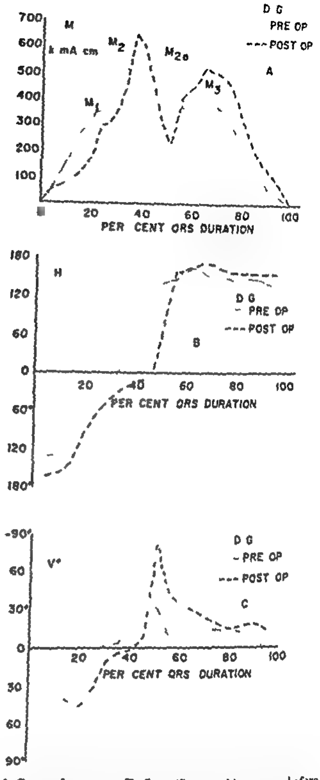


Fig 4 Curves for patient D G a 47 year old woman before and 13 days after closure of secundum defect The RV and PA pressures were normal and the flow ratio was 3 4 M decreased and M and M increased PO Peak M disappeared The H curves were normal but there were significant changes in the V curves The sequence was 348562 AO and 34856 PO

pointed more toward the right and somewhat less upward (columns 1, 2 and 3, Table III) M_1 also occurred somewhat earlier in the Group B patients The M_1 magnitudes were small as would be expected for the septal vector For both groups there were small counterclockwise and downward shifts PO There was a small decrease in M_1 in Group B PO The ratio M_1/M_3 increased in two cases but decreased in four, with a mean decrease of 9 per cent

Free wall excitation M_2 Table III shows that the M_2 magnitudes for Groups A and B were

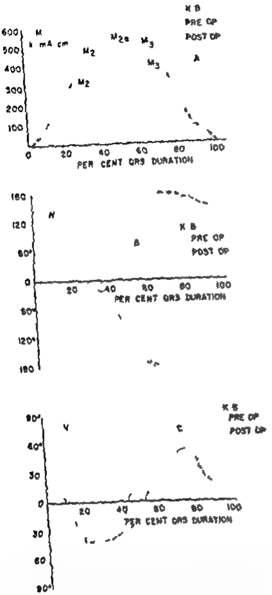


Fig 5 M H and V for patient K [redacted] a 10 year old boy Pressures were normal and the flow ratio was 2 0 There was anomalous pulmonary venous drainage with a sinus venosus defect. At the time of M there was little change in angles The sequence changed from 7841476 to 743 6

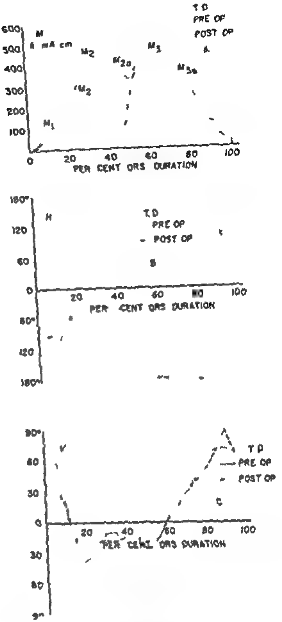
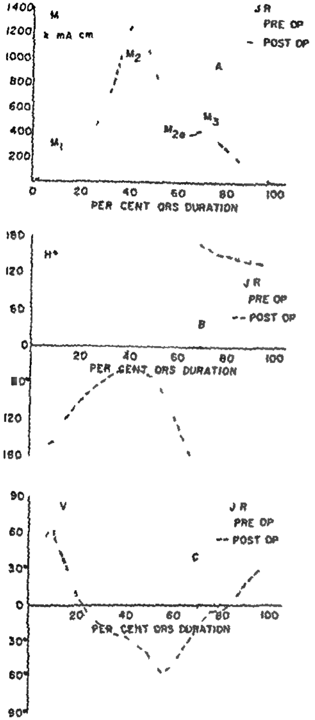


Fig 6 Curves for T D a 23 year-old woman before and 18 days PO The right ventricular pressure was 44 mm Hg and the flow ratio was 6 0 The sequence changed from 743"6 to 7343 65

significantly smaller than normal with Group B magnitude only about 60 per cent that for Group A These vectors were pointed to the left slightly anterior and downward The M_2 peaks occurred earlier than for the normals

After surgery there were increases in M_2 for both groups but neither returned to normal There were generally small clockwise rotations of the M_2 vector with little change in vertical angle Six Group A and three Group B surgical patients had M_4 peaks The magnitude increased in all cases PO The ratio M_2/M_3 increased in four of the six Group A patients and in two of the three Group B Fig 3 shows a typical increase in M_2

The hypertrophy peak M_{2a} We designate this peak the hypertrophy vector because it did not appear in any of the normals sometimes disappeared after closure of the ASD and occurred at a time appropriate for RVH Six patients in Group A had an M_2 peak occurring at a mean time of



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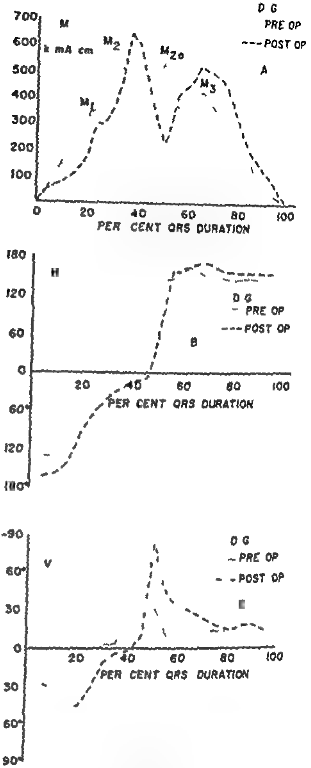

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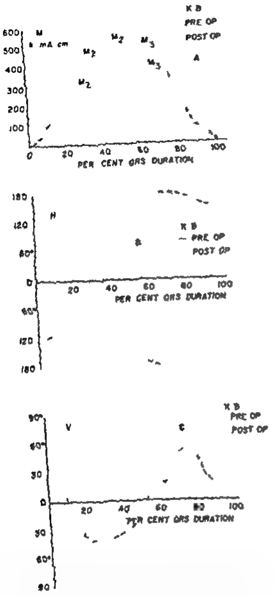
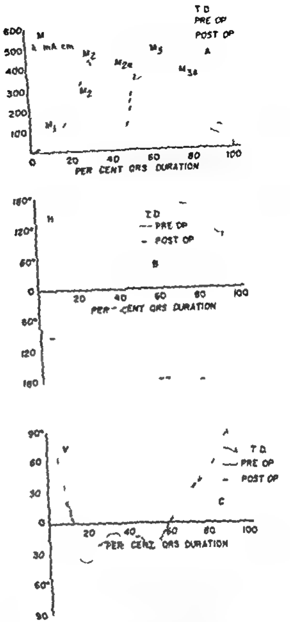


Fig 5 M H and V for patient K B a 10-year old boy Pressures were normal and the flow ratio was 2 0 There was anomalous pulmonary venous drainage with a sinus venosus defect At the time of M there was little change in angles The sequence changed from 784146 to 74376



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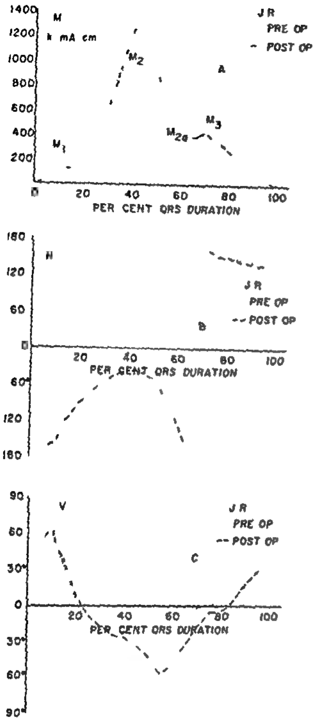

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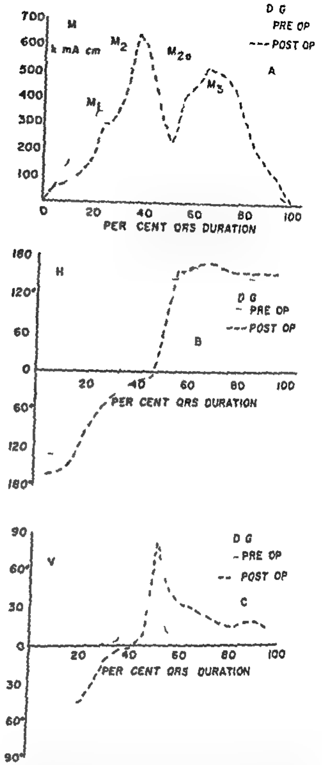

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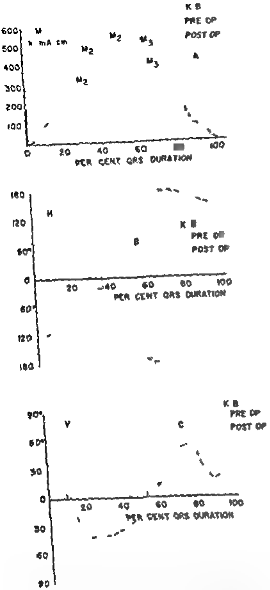

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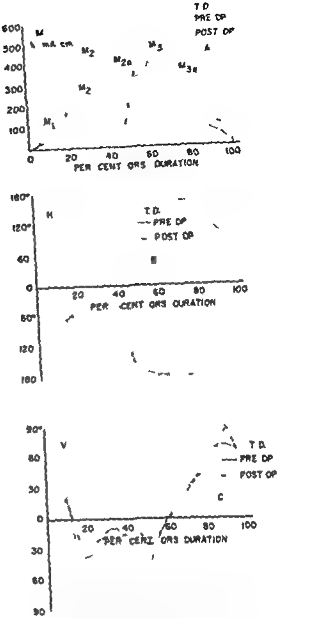

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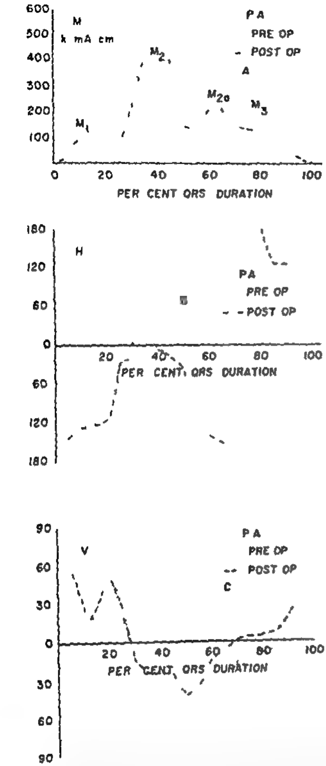

Fig 7 M H and V for P A a 35 year old woman before and 10 days after repair of a secundum defect The pressures were normal and the flow ratio was 4 0 The sequence changed from 7814326 to 784376 The late right anterior swing of the vector corresponds to the sector 3 position

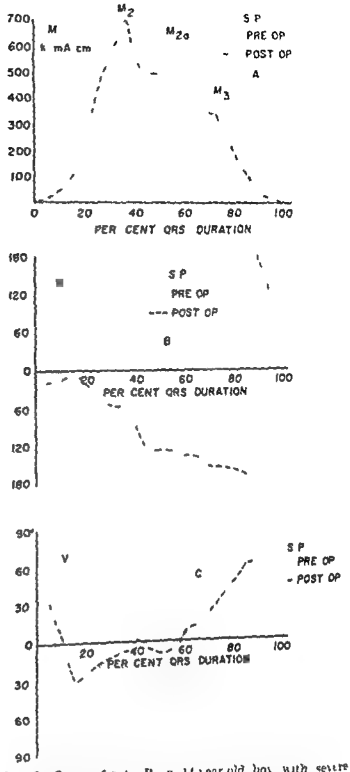

Fig 8 Curves for S P a 14 year old boy with severe pulmonic stenosis and a small secundum ASD taken before and two months PO The right ventricular pressure was 100 mm Hg and the flow ratio was 1 1 The horizontal vector was initially directed to the left and rotated in a clockwise fashion almost linearly The sequence changed from 437376 to 8437C The duration changed only from 106 to 105 msec

53 5 msec or 55 5 PQD (column 2 Table III) These vectors pointed to the right anterior or posterior and generally downward The five Group A surgical patients had the M_{2a} peak AO, but it disappeared in three of these PO (Figs 3 to 5) The values in columns 4 and 5 in Table III show M_2 values only for the two patients who retained the peak PO In these cases the magnitude increased with a counterclockwise rotation of the vector in the horizontal plane In these two cases the peak occurred much later than in the other three but decreased in time PO The direc

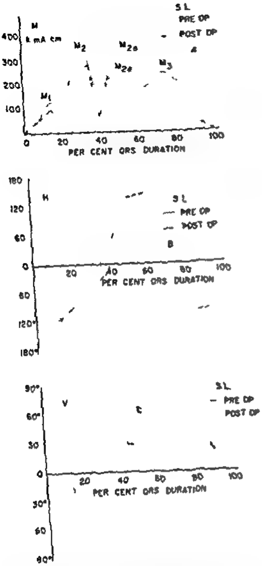

Fig 9 M H and V for a 16 year-old girl S L with combined secundum and primum defects before and 17 days after surgery Right-sided pressures were normal and the flow ratio was 5 3 The H curve is normal in shape but the shift from right posterior to right anterior occurs relatively early in QRS The V values are mostly negative corresponding to a superior direction of the vector The sequence changed from 34848567 to 348678 (Sectors 5 to 8 correspond to a superior direction of the vector) The duration dropped from 11° to 93 msec

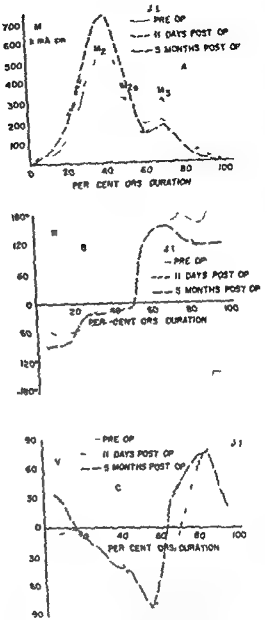

Fig 10 Curves for J I, a 26-year-old woman before 11 days after and 5 months after repair of secundum defect Pressures were normal and flow ratio was 2.7 See text for discussion

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Four of the Group B patients had an M_2 peak The mean magnitude was somewhat greater than for Group A In three of the four patients the vector pointed to the right anterior but in one it was to the left and slightly posterior In Group B M_2 was larger than M both before and after surgery None of these M_2 peaks disappeared PO and became somewhat larger (Table III columns 6 and 7) In these surgical patients the vector swung clockwise in one case counterclockwise in another, and remained essentially unchanged in the third The peaks occurred somewhat earlier PO but were at a later percentage of QRS duration because of the decrease in duration PO The curves for one of the Group B patients are shown in Fig 6

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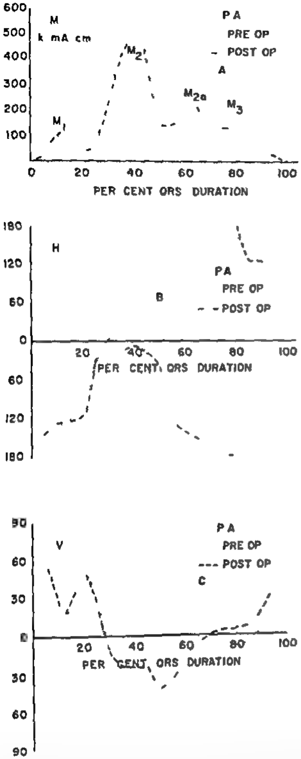

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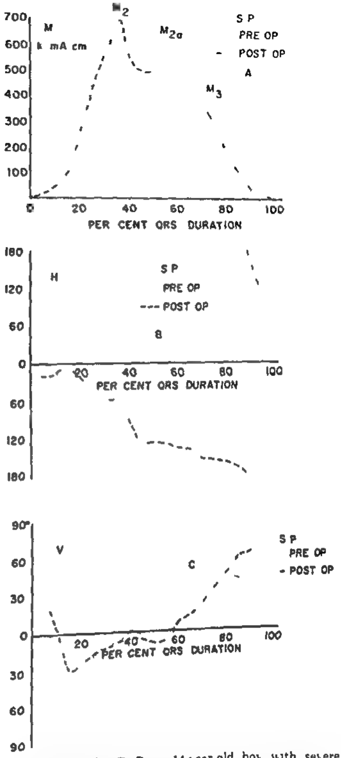

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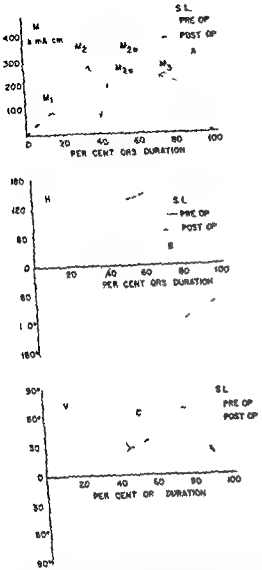

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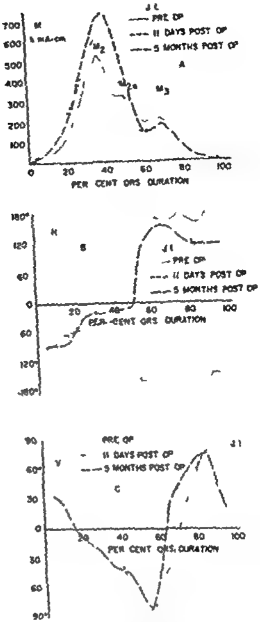

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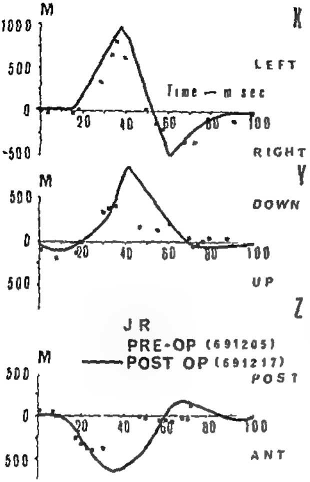

Fig 11 M M and M during QRS for same patient as in Fig 3 Twelve days after surgery the curves became essentially normal

values were rather small with no difference between the mean values for Group B and normals The mean value for Group A was somewhat smaller For both groups the M_3 vectors were pointed to the right and somewhat anterior or posterior In the normals, $H_3°$ was 98° representing a direction to the posterior and slightly to the right M_3 occurred later in the patients than for the normals

For both Groups A and B there were small mean increases in M_3 PO with little change in direction The M_3 peaks occurred a few milliseconds earlier PO Although QRS duration decreased PO the various peaks lined up fairly well when plotted as a percentage of QRS duration (Fig 7)

The Group B patients with elevated RV pressures tended to have large broad M curves with the vector directed anteriorly and downward during a larger proportion of the QRS interval than the normals or the Group A patients One of these (T T), who had anomalous pulmonary venous drainage and a right ventricular pressure of 50 mm Hg, had vectors directed almost entirely anterior and downward Fig 8 shows curves for a Group B patient In this case there was an unusual dip in the V° curve which disappeared PO Another Group B patient, J S, had a RV pressure of 64 mm Hg and a PA pressure of 63 mm Hg The M curve was broad with M_1, M_2, and M_3 appearing merely as extrusions of the curve H° changed slowly and steadily from 0° to −180° between 30 and 90 PQD No PO data were obtained on this patient Fig 8 shows the results for S P, a 14 year old boy with severe pulmonic stenosis and a small secundum ASD (not included in either Groups A or B) Follow up studies done 2 months later showed only small changes in vector magnitude and direction

Changes in vectors in patients with primum defects Four patients with primum defects were studied Of these two had surgery These patients also had three or four peaks in their M curves which changed after surgery In Fig 9 M_2 is smaller PO but in the other case M_4 was larger Preoperatively, for all patients M_1 was directed to the right anterior and slightly superior or inferior There were small decreases PO

The mean M_2 value was 366 k mA cm which was much below the normal value of 928 k mA cm In three of four cases the H° curve was similar to that shown in Fig 9 In the fourth (W R) the vector stayed in the right anterior direction from 35 PQD on This patient had a very large primum defect with a cleft mitral valve and right ventricular hypertrophy The QRS duration dropped from 147 to 139 msec Changes in H° and V° were small PO All had V° values which were mostly negative

Two patients had M_2 peaks both directed into sector II The mean M_3 value was 312 k mA cm and M_3 pointed into either sector 8 or 7 M_3 *increased somewhat* PO with a clockwise shift of $H_3°$ but with little change in $V_3°$ There were drops in t_3 of 14 and 20 msec in the two surgical *cases*

Follow up studies Two patients were remeasured some months PO to see if there were further changes Fig 10 shows that M_2 and M_3 increased 11 days PO but M_{2a} disappeared Five months later M increased still further but M_3 dropped to about the preoperative value The H° curve had the RVH pattern 11 days PO but became normal

8 months later The V curves were similar in shape but there were differences in time relationships The sequences were 843767 43265 and 84126, in order

In this patient the three midanterior electrodes were on the midsternal line AO After surgery because of the midline incision the electrodes were placed one inch to the right of the midsternal line To assess the effects of electrode displacement the VCG taken 5 months later was done with both placements of the center electrodes The only difference was about a 5 per cent change in magnitude in M_y As mentioned earlier the lead system used is relatively insensitive to changes in electrode position

In another patient with a secundum defect (G C) M M and M_y all increased 10 days PO but dropped below preoperative values 10 months later There were only minor changes in vector directions In earlier studies in a different group of patients Sloman[4] found that 6 months or more after surgery there was less right axis deviation a diminution of right ventricular preponderance and a diminution in heart size The mean cardiothoracic ratio fell by 50 per cent

Changes in P waves The P wave magnitudes (P M) were calculated from the peak values of M M and M These values were not necessarily synchronous and did not distinguish between deflections due to right and left atrial excitation

P M dropped PO in all but one patient The mean decrease was 25 per cent of the PO value (126 to 83 k mA cm) In all cases AO H° was in the range −23 to −56° (mean = −40°) corresponding to a left anterior direction In all cases there was a leftward shift in the horizontal vector The mean value of H PO was 16 The mean values of V° AO and PO were 40 and 2° respectively On the average therefore the P vector dropped in magnitude and moved leftward and upward PO The drop in P wave magnitude agrees with earlier findings

T waves In Groups A and B the peak T deflection dropped in magnitude in seven of eight cases The mean change was a drop from 243 to 191 k mA cm In general there was a leftward shift PO from mean H = −8° to 36° Mean values of V° changed only from 25° to 22° For the two patients with primum defects T M increased moderately

Table IV Correlations of ECG data with flow ratio and right ventricular pressure

Factor	*Flow ratio*		*RV pressure*	
	r	*P*	*r*	*P*
QRS duration AO	.65	01−05		
Δ duration (msec)	−.59	05−10		
PA systolic pressure			.54	.05−10
M AO			−.74	.05−10
M /M AO			−.87	001−01
t (msec)			0 62	10
Δ t,(msec)	−.97	001−01		
Δ t (%)	−.99	001		
M_y AO			0 52	05−10
M /M AO			0 62	01−05
Δ R_y	−.71	01−05		
Δ (R/S) (%)	−.86	01−05	−.82	.01−05
Δ Q (%)			−.84	001−01

Dipole moment components M M_y and M For the normals M and M_y usually had a QRS configuration but in some cases either Q or S was missing For M the wave shape was QR except for three subjects in whom there was a terminal S wave Mean values in k mA cm were

M = −53 685 −166
M_y = −65 588 −101
M = −310 373 −60

The wave shapes for the patients were much less regular especially the Y and Z leads In four cases the Y lead showed double peaked R waves In five cases the Z lead had a QQ R complex with the second negative (anterior) deflection occurring fairly late in the complex The mean values for Groups A and B were

AO M = −31 389 −343 M_y = −77 274 −150 M = −186 122, −169
PO M = −39 467 −350 M = −41 323 −129 M = −244 87 −14

It is seen that R R_y Q and R were smaller than for the normals After repair of the ASD R R_y and Q increased somewhat but R became smaller Also S S_y and S were larger than for the normals After surgery S increased still further but S and S became somewhat smaller Changes in dipole moment components for J R are shown in Fig 11 In the patients with primum defects the Y leads were mostly negative

Correlation coefficients Although there were

only nine surgical patients in Groups A and B we computed some correlation coefficients to see if there were any trends More samples were available for correlations with preoperative data only Correlations were made with both flow ratio and right ventricular pressure Table IV shows the results for correlations where $r \geq 0.50$ and $P \leq 0.10$ for Groups A and B For these groups there was a fair correlation between preoperative QRS duration and flow ratio, as well as for the change in duration after surgery and flow ratio When all patients were included, the correlation between QRS duration and flow ratio was $r = 0.83$ $P < 0.001$ Although the correlation between QRS duration and right ventricular pressure was weak, there was a general increase in duration for higher values of RV pressure Using correlation analysis for two variables the following equation was derived

$$y = 80.84 + 3.88\,X_1 + 0.18\,X_2$$

where y = QRS duration (msec), X_1 = flow ratio and X_2 = RV pressure (mm Hg)

For a flow ratio of 1 and a RV pressure of 27 mm Hg the duration would be 89.6 msec The measured QRS duration for 15 normals was 88.3 msec In some of the laboratory reports pressures were stated as being within normal limits We used a value of 27 mm Hg for these patients as listed in a standard handbook[11] The equation states that an increase in flow ratio by one unit causes an increase in QRS duration of 3.9 msec and an increase in RV pressure by 10 mm Hg causes an increase in duration of 1.8 msec Other workers have also found a correlation between QRS duration and flow ratio using the Helm lead system[1]

QRS durations were determined from the times between earliest and latest deflections in expanded X Y and Z leads The durations read from standard ECG's were not adequate for this purpose The change in ratio of R to S in the Y lead correlated well with both pressure and flow ratio There was a high correlation between the change in t_1, the time of occurrence of the M_1 peak, with flow ratio There were only six data points in this relation but they all fell very nearly on a straight line The ratios of peaks M_1 and M_2 to M_3 correlated better with pressure than flow ratio

Discussion

In 1956 Brody showed on theoretical grounds, that the effect of the intracardiac blood should be to increase potentials due to excitation radial to the cavity and to attenuate potentials due to tangential excitation[13] These findings were later confirmed experimentally[7,14] and found to be of considerable importance Normal intracardiac blood in the dog causes an apparent increase in M_1 by a factor of 3, in M_2 by a factor of 2.5 and a decrease in M_3 by about 25 per cent M_1 and M_2 are radial dipoles corresponding to septal and free wall excitation M_3 is tangential and is the late basal excitation vector It seems reasonable to suppose that the abnormal blood volumes in ASD should affect the VCG and that changes occurring shortly after surgery should be due to restoration of normal volumes Right ventricular hypertrophy often exists, especially in ASD which has persisted for several years It is unlikely that hypertrophy would regress to any sizable amount within two weeks after surgery, although data on this point are lacking The ECG abnormalities remaining after surgery should then be due mainly to the RVH The ECG accompanying ASD has often been ascribed to right bundle branch block but no evidence of this has been found upon examination of the conducting system[13]

Dogs in which aortocaval fistulas were created developed cardiac dilatation and hypertrophy[15] Three months after closure of the fistulas, ventricular volume had regressed to about halfway to normal After 6 months the ventricular mass was still greater than normal[16] After closure of an atrial septal defect the blood volume in the right ventricular cavity must be reduced A recent report stated that RV blood volume in ASD was twice normal but returned to normal PO[17] It has been shown that contractility is not impaired by volume overload in ASD[18]

Changes in the ECG with hypertrophy or pressure overload can be explained by increases in muscle mass resulting in a greater effective dipole moment of portions of the heart In these cases good correlations have been found between the amplitude of the VCG and systolic pressures[19,20] In ASD the essential change is dilatation of the right ventricle, often accompanied by an increase in muscle mass VCG changes due to ventricular dilatation have been attributed to

changes in heart position to modification of the sequence of activation and to changes in heart shape and geometry resulting in alterations in cancellation of vectors[2, 7] Ventricular overloading may cause phase differences in the sequence of depolarization causing changes in spatial vector magnitude[21] Other hypotheses for the effects of dilatation are an increase in the length of the conduction pathway decreased cross sectional area of stretched fibers or right bundle branch block[2] Atrial septal defect may be accompanied by distortions of the left ventricular geometry as well as of the right[2, 3]

Another possible explanation is that the right ventricular vector is enhanced by the increased volume of this chamber i e the Brody effect[3] is increased by the greater blood volume We found in eight of nine patients with secundum ASDs that the M_z vector increased by an average amount of 23 per cent after surgery In ASD the larger RV vector may partially cancel the LV vector giving a smaller resultant After the ASD was repaired with reduction of RV blood volume the smaller RV vector would offer less cancellation and the resultant vector would be larger Other studies have shown that the peak vector is smaller in ASD[2]

Benchimol and Tio found a postoperative decrease in the RV vector and an increase in the maximal QRS vector They believe that other factors than an increase in muscle mass are responsible for the VCG changes in RVH and that these are related to pressure or volume overloading The peak vector spatial magnitude was greater than normal in LVH but below normal in RVH[2, 29]

In studies on the effects of pulmonary embolism on the dog ECG Rasmussen and Michelsen[24] mentioned the possible role of intracardiac blood and heart dilatation They did not think that the observed changes resulting from pulmonary obstruction i e counterclockwise rotation of the horizontal QRS loop and reduction in Z lead voltages were consistent with the Brody theory We believe that the reduction in spatial and Z lead voltages in ASD may be due to an increased RV vector If this hypothesis is correct one would expect that after surgery and diminution of the RV vector there would be a leftward (counterclockwise) shift of the net horizontal vector We found however that there was generally a small rightward shift of the M_z vector The mean change in angle $H_z°$ was from $-6°$ (horizontal vector pointing to the left and slightly anterior) to $-23°$ At the time of the M_z vector there was a mean shift in direction by 34° to the left and 6° inferiorly* In one other patient (S P) with severe pulmonic stenosis and RV pressure of 100 mm Hg there was a change in $H_z°$ from $-101°$ to $-47°$ For the Group A patients the mean change in $H°$ was negative (clockwise) up to about 47 PQD and positive (counterclockwise) from 48 to 82 PQD For the Group B patients with higher RV pressures, $H°$ changes were negative up to 37 PQD and positive from 38 to 77 PQD From 38 to 62 PQD the mean change in the latter group was 38° For both groups there were more decreases in M than increases up to 17 PQD after this time there were more increases than decreases

If the changes in M are related to changes in intracardiac blood one must consider the direction of the excitation relative to the RV cavity as well as interaction with the LV vectors Neglecting possible changes in LV volume or geometry we then have a variable RV vector and a fixed LV vector at any instant relative to preoperative conditions We have attempted to explain our findings in this light using the excitation data of Boineau Spach and Ayers[15] Although these data are for the dog heart it has been shown that the excitation of the dog and human hearts are similar[3, 32] In Fig 3 of Boineau and associates[15] for the normal heart we let 35 msec equal 100 per cent duration and in Fig 6 for the dog with ASD 44 5 msec equals 100 per cent

As stated above M generally decreased PO up to 17 PQD Also Table III shows that M_I was below normal for the Group B patients and decreased somewhat further PO Boineau and associates state that early excitation in the dogs with ASD was similar to the normal pattern with excitation starting in the middle portion of the left side of the septum and the lower anterior right septal surface This results in two oppositely directed vectors with the left to right vector predominant because of the earlier excitation of the left septum and greater muscle mass involved Since these vectors are both radial to the cavities

*This shift in H_m differs from Table III because it includes all surgical patients whether or not M_m was present PO

the intracardiac blood should augment each vector The two vectors tend to cancel out since they are opposing An increase in right cavity blood volume should increase the potentials due to both vectors but would have a greater effect on the right to left vector since this is closer to the right cavity An increased right to left vector would then increase cancellation of the left to right vector and the net vector would be smaller The fact that M_1 was about normal for the Group A patients but below normal for Group B indicates that hypertrophy was probably more significant than the blood volume at this time In addition, M_1 did not increase PO which should have occurred if intracardiac blood were augmenting the RV vectors

The M_2 vector occurred at 43 PQD for the normals and 33 to 36 PQD for the patients Corresponding times in msec were 38 and 32 to 34 M_2 was much below normal and increased PO For the normals this coincides with the 13 to 21 msec range in Fig 3 of Boineau and associates[11] This excitation is described as 'encirclement of ventricular cavities in an apex to base direction with subsequent endocardial to epicardial spread The wave fronts in the predominant left (inferior) ventricular mass are associated with inscription of the R loop

The description of Durrer and associates[31] of right ventricular excitation states that rapid invasion of the septum and adjoining free right ventricular wall occurs and results in epicardial breakthrough in the area pretrabecularis after about 20 msec The isochrones are not concentric but rather activation proceeds in a regular more or less *tangential* way, reaching ultimately the pulmonary conus and the posterobasal area at 60 to 70 msec Durrer[13] states that activation in the right ventricle is more radially oriented in the apical part and tangentially oriented in the basal half since the Purkinje system is not as dense in the basal portion He considers that there is a gradual transition at about 35 msec

For the time period 35 to 40 msec for the human being Scher[3] stated that the major *source of potentials* is in the apical lateral, and anterior left wall but that some opposing inside out activity persists in the basal right wall

Whether the right ventricular excitation is radial or tangential makes a great deal of difference from a theoretical standpoint since opposite effects of intracardiac blood would occur After epicardial breakthrough, it would seem that further depolarization might be a combination of radial and tangential spread In this case, intracardiac blood would enhance potentials due to radial spread and decrease those due to tangential movement, creating the appearance of radial spread

When two vectors make an acute angle with each other an increase of either vector will increase the resultant vector If the two vectors have an obtuse included angle, however, an increase of one vector might either decrease or increase the resultant[34] If μ is the ratio of the RV to the LV vector and θ is the included angle, then an increase in the RV vector will decrease the resultant if μ is less than $\sin \alpha$ but will increase the resultant if μ is greater than $\sin \alpha$ where $\alpha = \theta - 90°$[34] In either case there is a clockwise rotation of the vector There are then six combinations which could determine the effects of changes in intracardiac blood on the RV vector and its action in opposing or adding to the LV vector whether the RV vector is radial or tangential and whether the included angle is acute, obtuse with $\mu < \sin \alpha$ or obtuse with $\mu > \sin \alpha$ There are only two possible combinations with which our results would agree for the M vector i e a postoperative increase in M_2 with a clockwise rotation of the vector If the RV excitation is tangential at this time the decrease in RV blood volume PO would increase the RV vector If the angle between the RV and LV vectors is acute the increased RV vector would increase the resultant vector with a clockwise rotation This could also happen with tangential excitation and $\mu > \sin \alpha$ For the latter situation to exist, the RV vector would have to be a significant fraction of the LV vector[34] Because the excitation waves surround both cavities at the time of M_2 it is difficult to estimate the individual magnitudes and directions of the RV and LV vectors It is not impossible that the two vectors could make an acute angle with each other We are not aware of any data which could provide information on this point

It is not possible to rule out rotation of the heart after surgery If the RV excitation is radial a decrease of the RV cavity blood would decrease the RV vector and increase the resultant vector This should result in a counterclockwise or left

ward shift of the vector unless the heart rotates sufficiently to compensate for this Chen and associates[1] found varying degrees of posterior and leftward displacements of the interventricular septum in patients with secundum ASD s by means of biplane cineangiograms If the heart resumed a more normal position after surgery this would result in a rightward shift of the vectors

The M_2 vector occurring at a mean time of 54 PQD did not appear in any of the normals This time corresponds to the end of the 21 to 25 msec range of Fig 5 in Boineau and associates [8] During this interval in the ASD dogs the activation front formed a circle encompassing both ventricular chambers in the two central planes Excitation of the left ventricular free wall was nearly completed except in the high basal areas Our data show that the resultant vector was in most cases directed towards the right anterior and downward This represented a swing of the vector back to the right anterior which did not occur in the normals In general after surgery there was a small leftward (counterclockwise) rotation of the horizontal vector The M peak could be caused by a combination of right ventricular hypertrophy and dilatation The fact that M_{2a} disappeared in three cases PO must have been due to reduction of the dilatation factor When M_2 persisted PO it either stayed the same or increased in magnitude Because of these conflicting results it is difficult to theorize about what is happening Marked increases in M_2 were accompanied by a ccw rotation whereas marked decreases were accompanied by a cw rotation

In the Group B patients with higher RV pressures the changes in M_2 and H_2 were smaller than for the Group A patients indicating that the intracardiac blood effects were secondary to the existence of RVH There was a signif icant difference in H ° in the two groups The presence of the M_2 peak may correspond with the presence of two potential maxima on the thorax during the latter half of QRS in patients with secundum ASD [7,16]

The late M_3 vectors occurred at a mean time of 67 msec as compared with 59 msec for the normals Because of the longer durations of QRS in the patients however the time percentages were nearly the same (69 and 67 PQD respectively) For all patients M_3 was somewhat below normal but increased to normal PO The main difference from normal was the more rightward orientation of the horizontal vector (Table III) This difference remained PO At this time, in the dogs with ASD [11] there was invasion of the crista supraventricularis and the high outflow tracts Activation of the left ventricle and center of the ventricular septum was completed during this interval As this was essentially tangential spread the increase in M_3 after reduction of RV blood volume is consistent with the Brody effect The effect was small because of the mass of the tissue activated and its mean distance from the cavity For the normals at this time there was still activation of the basal LV wall resulting in a more directly posterior vector

Table V Ratios of peak vector component deflections Ratio (ASD/normal)

Deflection	*Blumenschein et al.*	*AO*	*PO*
Q		0 58	0 74
R	0 72	0.56	0 68
S	2.20	2.07	2.23
Q		1 18	0.63
R_y	0.51	0 47	0.55
S	1 60	1.50	1.28
Q_z	0.85	0 60	0 79
R_z	0 43	0.33	0.23
[illegible]		2.82	2.37

In this table +R is to the left +R_y is inferior and +R is posterior Blumenschein and associates use the opposite convention for the Z lead

Blumenschein and associates[26] showed that the peak deflections of the X Y and Z leads were different for children with ASD and for normals We have computed mean values of these deflections and the comparison with the data of Blumenschein and associates is shown in Table V They define R as the maximum anterior deflection but did not distinguish between early and late deflections. We have listed their anterior deflections as Q as this seems to correspond more closely with our data It is evident that there is fairly good agreement between the two sets of data even though one set was for children and the other included mostly young adults Columns 3 and 4 of the table give pre and postoperative values for our own results The table shows that Q R R_y S_y Q and S change

toward normal postoperatively, although in most cases the ratios still differed considerably from 1 0 Only three of the normals had S_1 deflections, but six patients had S_1 deflections comparable to or larger than Q_1

The peak spatial vectors occurred at different times during QRS For the normals, M_2 was always the largest peak For the six Group A surgical patients, three had M_2 as the largest peak, *two had M_{2a} and in one M_3 was the largest* After surgery for the two patients with M_{2a} peaks, the largest changed to M_2 in one case and M_3 in the other For the three Group B surgical patients, M_{2a} was the largest peak in one case and M_3 was largest for the other two M_3 changed to M_{2a} PO in one case When comparing spatial vectors it is necessary therefore, to use values at corresponding times during QRS

This may account in part, for the difference between our findings and those of Hisamatsu[3] who found small reductions in the maximum spatial QRS vector one month PO but increases in one year In patients with normal RV and PA pressures the vector loops had approached normal one month PO The maximum vector was smaller in patients with elevated pressures Hisamatsu[3] found counterclockwise rotation of the QRS axis in the horizontal plane Another reason for the difference in results may have been due to the lead systems used It has been shown that the lead system used in this study is considerably more accurate than the Frank This system uses 24 thorax electrodes instead of five It also has three electrodes on the right anterior chest wall whereas the Frank system has none Vectors directed toward (or away from) the right anterior wall will therefore, be underestimated by the Frank system This is true also for vectors parallel to the anterior surface of the thorax Model studies have shown that for a horizontal dipole near the anterior surface the points of maximum potential do not lie on a line through the dipole but rather on a curved path which intersects the anterior wall at varying distances to the left and right of the midsternal line depending on the distances of the dipole from the body surface [10, 11] In RVH the right ventricle may lie against the posterior aspect of the sternum and the anterior chest wall[12]

Table III shows that M_1 and M_2 occurred earlier in the patients, particularly in Group B than for the normals but M_3 occurred later than normal We are unable to explain these time differences It was found that the velocity of radial spread in the wall of the hypertrophied right ventricle was three times normal[13] It is possible that an increased conduction velocity might result from the lower internal resistance of the hypertrophied cardiac cells[4] The later occurrence of M_3 may have been due to the greater thickness of the outflow tract of the right ventricle requiring more time for excitation[15]

Summary

Spatial dipole moment of the heart (M) was measured in patients before and 1 to 2 weeks after repair of atrial septal defect In normals three peaks of M were found, corresponding to excitation of the septum (M_1), ventricular walls (M_2) and basal portion of ventricles (M_3) Most of the patients also had an M_{2a} peak at 52 to 56 per cent of QRS duration The patients with secundum defects were divided into two groups A and B depending on whether right ventricular pressure was less than or greater than 30 mm Hg

M_1 was smaller for the Group B patients than for the normals or Group A and decreased slightly after surgery M_2 was about half normal for Group A and one third normal for Group B After surgery M_2 increased for both Groups but was still below normal There were small mean clockwise rotations of the M_2 vector in the horizontal plane PO The M_{2a} vector pointed to the right anterior or posterior and generally downward In three Group A patients the M_{2a} peak disappeared PO but in two others it increased in magnitude with a counterclockwise rotation in the horizontal plane In the Group B patients, M_{2a} increased in all cases The M_3 vectors generally increased slightly in magnitude postoperatively M_3 pointed posteriorly in the normals but to the right in the patients with little change in direction after surgery Both P and T curves dropped *in magnitude after surgery The changes* observed may be due in part to restoration of right ventricular blood volume towards normal after surgery The remaining VCG abnormalities should be due to right ventricular hypertrophy

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Attacks of ventricular fibrillation and unconsciousness in a patient with prolonged QT interval. A family study

J. M. Chaudron, M.D.
F. Heller, M.D.
H. B. Van den Berghe, M.D.
E. G. LeBacq, M.D.
Haine St. Paul, Belgium

In 1957 Jervell and Lange Nielsen[1] described a syndrome characterized by (1) perceptive bilateral congenital deafness of the Scheibe type, (2) a prolonged QT interval on the electrocardiogram (ECG), and (3) spells of fainting ascribed to disturbed ventricular rhythm.

To our knowledge, 30 such cases have been reported so far; they are discussed in our comments.

A similar syndrome of prolonged QT interval and syncopal attacks without deafness has been described in 1963 by Romano, Gemme, and Pongiglione[2] and later by Ward.[3]

Simultaneous study of both syndromes is justified by their similarities.[4]

Few cases have been documented with ECG recordings during the attacks or with familial study.

This paper reports a new case of Romano-Ward syndrome with ECG findings during long spells of unconsciousness with the family history throwing some light upon the mode of transmission.

Case report

M. F. D., a female born in 1959, had her first attacks of unconsciousness at the age of 5 years; a diagnosis of epilepsy was made and treatment was instituted with anticonvulsants. New attacks occurred in the following years, especially in the spring and autumn, often induced by vigorous exertion (racing, swimming) or by menstruation.

At the age of 14 years, two violent episodes of convulsions occurred during two consecutive menstrual periods, preceded by a feeling of cardiac arrest.

From the University of Louvain, Medical Department, Hôpital de Jolimont, and the Laboratory of Cytogenetics.

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Reprint requests: Dr. J. M. Chaudron, Hôpital de Jolimont, 7161 Haine-St. Paul, Belgium.

On April [illegible] 1973, she was admitted to Jolimont Hospital for status epilepticus. The ECG shows strips of ventricular flutter and multifocal ventricular tachycardia started by ventricular ectopic beats (Fig. 1) with spontaneous improvement and immediate recurrence.

The patient was transferred to the intensive-care unit and treated with 200 mg. of intravenous lidocaine, followed by lidocaine infusion, 2 Gm. in 24 hours, with good results.

Propranolol, 20 mg. four times a day, was started the next day; after she regained consciousness, her successive ECG's were typical of Romano-Ward's syndrome (Fig. 2) as follows: (1) prolonged QT interval (0.46 sec. against the upper normal limit of 0.38 sec. assessed by Bazett's formula), (2) biphasic large T waves, and (3) ample U waves. No further ectopic beats were noted, and the patient was transferred to the medical department.

Four days later, a bout of ventricular flutter occurred (Fig. 3) with convulsions, loss of consciousness, and bladder incontinence; it disappeared after external cardiac massage and positive pressure respiration for a few minutes.

The following day, numerous spells of ventricular tachycardia and even short-lived ventricular fibrillation were recorded on the ECG without the patient being aware of the arrhythmia.

Treatment with intravenous digoxin was then started, followed by oral digitoxin, 0.1 mg. per day, and propranolol, 120 mg. per day. The attacks did not recur so far with this treatment.

The patient was extensively investigated during her ensuing stay in the hospital.

Cardiac auscultation revealed a short systolic murmur on the left side of the sternum interpreted as being anorganic.

Mechanical systole was normal, while electrical systole was prolonged, the second heart sound corresponding to the middle of the T wave (Fig. 4).

The chest x-ray film was within normal limits with a normal heart size.

Laboratory investigations gave normal results except for slight polymorphonuclear leukocytosis and a discrete increase of serum transaminases and creatine phosphokinase after the attacks. Main laboratory data were as follows: erythrocyte sedimentation rate, 4 mm. per 1 hour; hemoglobin, 15.4 Gm. per cent; hematocrit, 44 per cent; red blood cells, 5,100,000 per

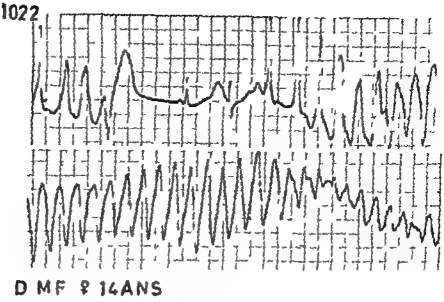


Fig 1

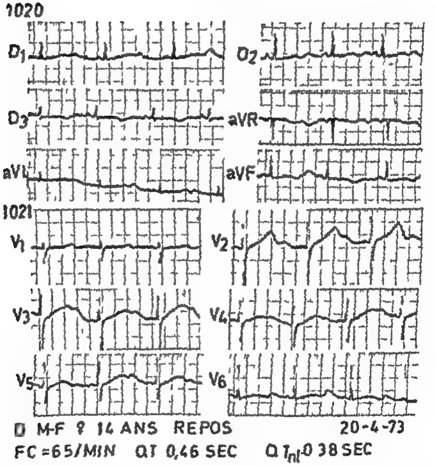


Fig 2

cubic millimeter white blood cells 7 200 per cubic millimeter differential count neutrophils 71 lymphocytes 28 mono cytes 1 platelets 320 000 per cubic millimeter Na 141 mEq per liter K 4 1, Cl 102 HCO 23 Ca 10 2 mg per cent P 4 3 mg per cent pH 7 38 PCO_2 39 mm Hg red blood cell Mg 5 1 mg per cent creatinine 0 7 mg per cent cholesterol 210 mg per cent triglycerides 85 mg per cent lipidogram normal iron 75 μg per cent Iron Binding Capacity 270 μg per cent protein bound iodine 6 6 μg per cent uptake in vitro T RU 27 per cent T (tetrasorb) 8 3 μg per cent urine normal sediment normal and glucose tolerance test 80 130 125 100 115 and 100 mg per cent (Conn and Fajans tech nique)

The EEG recorded after syncopal episodes showed dys rhythmic spells with right temporal predominance after hyperpnea

The audiogram revealed a slight bilateral deficiency of transmission and a slight deficiency of perception inferior to

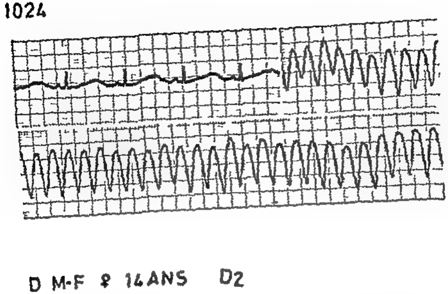


Fig 3

Fig 4

10 decibels apparently ascribable to nasopharyngeal infection

Chromosome number and morphology were completely normal (Dr Koulischer) Dermatoglyphics were normal (Dr Verresen)

Hemodynamic studies were performed by Drs Rousseau and Brasseur (Laboratoire d Exploration Fonctionnelle Cardiopulmonaire Cliniques Universitaires St Pierre Louvain) The results are recorded in Table I

Family study (Figs 5 and 6 Table II) Normal QT intervals are derived from Bazett s[11] formula

$$(QT = 0.4 \sqrt{RR} \pm 0.04)$$

and related to the heart rate (Fig. 5)

The patient s family study is especially rewarding One brother died suddenly at the age of three years during tonsillectomy A second brother was stillborn. The mother had three abortions.

Two other siblings are alive a sister aged 18 with an

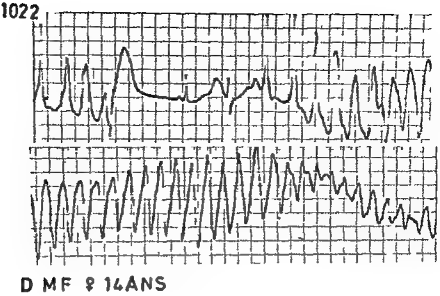
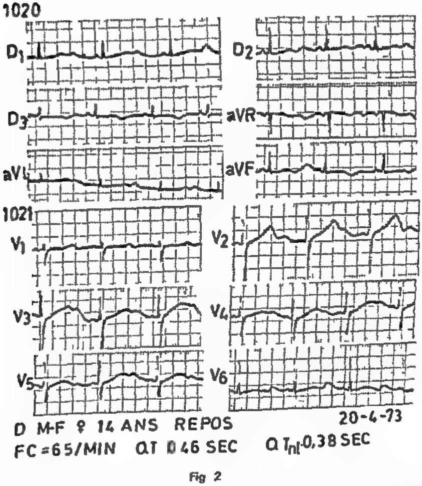


Fig 1



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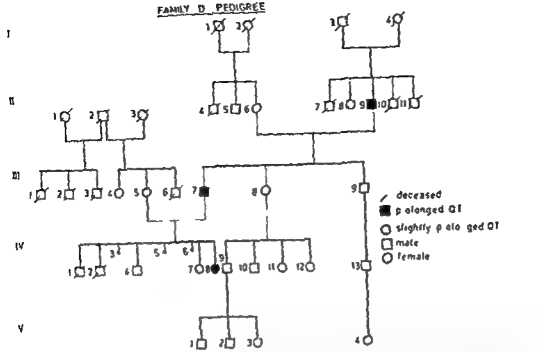

Fig 6 I (1) Died aged about 60 unknown cause (2) died aged 82 (3) died aged about 50 silicosis and (4) died aged 82 II (1) Died aged 33 unknown cause (2) died aged 80 (3) died aged 33 in confinement (4) died aged 80 (5) 77 years-old normal QT (6) 81 years-old normal QT (7) died aged 80 (8) died aged 80 (9) aged [illegible] prolonged QT (10) died aged 0 and (11) died aged 33 unknown cause III (1) Died in early childhood unknown cause (2) died in early childhood unknown cause (3) died aged 62 digestive tract cancer (4) aged 58 normal QT (5) aged 56 slightly prolonged QT (6) died aged 15 days unknown cause (7) aged 59 prolonged QT (8) aged 54 normal QT and (9) aged 51 normal QT IV (1) Died at birth (2) died aged 3 tonsillectomy (3) miscarriage (4) aged 27 normal QT (5) miscarriage (6) miscarriage ( ) aged [illegible] slightly prolonged QT (8) aged 14 prolonged QT (9) aged 29 (10) aged 27 (11) aged 25 normal QT (12) aged 18 and (13) aged 23 V (1) aged 5 (2) aged 3 (3) aged 2 and (4) aged 3 normal QT

brother treated for the same symptoms died suddenly when the parents stopped adrenergic beta blocker treatment

Ten families and seven isolated cases with this condition have so far been described[2,3] The first family is probably that recorded briefly by Gyllensward in 1957

An ECG recording during the attacks of arrhythmia is available in five cases only[3,7,5,26]

We were able to record several ECG s during syncopal attacks

The arrhythmia is either a typical ventricular flutter or multifocal ventricular tachycardia[27] initiated each time by a ventricular premature beat occurring during the vulnerable phase which is especially prolonged in this case of slow repolarization[7] QT prolongation varies from time to time and may be normal on occasion[25,3]

In some cases it is obvious only after exertion[3,22]

Jervell and Lange Nielsen[1] found no correlation between the degree of QT prolongation and the number or the severity of the attacks On the other hand Fraser, Froggatt and James[7] while agreeing with the Norwegian authors believe that greater prolongation is associated with an earlier age of onset and increased frequency of the attacks

In our patient the onset was more delayed (five years) than in other reported cases while QT and QU intervals are very long

Mode of transmission Jervell and Lange Nielsen s syndrome is due to an extremely rare gene the frequency is less than 1 per cent of the total number of children with severe perceptive deafness[9] Its inheritance is autosomal recessive Consanguineous mating is frequent among the parents

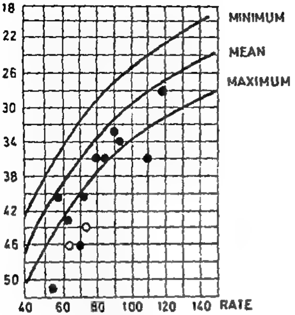

Fig 5 QT nomogram White circles patient s values black dots relatives values (According to Hegglin and Holzmann)

Table I

	At rest recumbent	At rest sitting	Exercise 50 W
VO (ml /min)		210	768
Cardiac frequency		74	96
Arterial O (ml %)		17 7	18 12
Arteriovenous gradient		5 02	9 4o
Cardiac output (L /min)		4 2	8 1
Systolic output (ml)		56	85
Pressures (mm Hg)			
Pulmonary artery	15	17	22
Pulmonary wedge pressure	9		

Conclusion slight increase of mean pulmonary artery pressure at rest and after a 50 W exercise

electrocardiographic QT interval prolonged at 0 36 sec for a cardiac rate of 108 per minute (normal QT 0 29 sec) and a brother aged 27 with a normal ECG (QT 0 33 sec normal 0 32 sec) the sister had some syncopal attacks in childhood but not the brother

The parents are good healthy and unrelated But their ECG is abnormal the father has a QT interval of 0 51 sec considerably longer than the predicted value of 0 40 sec the QT interval of the mother is 0 44 sec the calculated normal value being 0 38 sec They give no history of syncope The paternal grandparents are alive The grandfather s QT interval is prolonged at 0 46 sec (normal 0 36 sec) the grandmother s QT interval is at 0 36 sec (normal 0 32 sec)

The maternal grandmother died at the age of 30 years in confinement

Uncles and aunts of the patient are in good health with a normal ECG

Genetics In this family with no known consanguinity and no deafness four affected individuals belong to three different generations and male to male transmission is observed The mode of inheritance is compatible with an autosomal dominant gene

Dermatoglyphic Investigation (Dr Verresen) A dermatoglyphic investigation was performed because mention had been made of a dermatoglyphic abnormality in Jervell and Lange-Nielsen s syndrome[2] Qualitative and quantitative examination of the fingers and palmprints of several members of this family failed to reveal any significant anomaly and more specifically no increased number of arches could be demonstrated

Discussion

Fraser and associates[6,7] stated that the first probable cases of surdocardiac syndrome were reported by Meissner in 1856 and Morquio 1901

The first documented report by Jervell and Lange Nielsen[1] describes a Norwegian family in which four of six siblings had the association of QT interval prolongation and syncopal episodes All four children were deaf mutes three died suddenly at the age of four, five, and nine years, no ECG was recorded during the attacks

Levine and Woodworth[8] documented the case of an eight year old boy with the syndrome but stated that the pulse was noticeable during the syncopes

Fraser, Froggatt, and Murphy[9] after an extensive survey of deaf mutes in Great Britain and Ireland found nine new cases among 1,491 subjects

To our knowledge, so far, 30 cases of this syndrome have been reported[1,5,7,8,10,22] No sex predominance was found

The case of Jervell and Sivertssen[15] is the first to have an ECG recording and ventricular fibrillation in alternation with asystole documented during the syncopes

Romano Ward's syndrome of QT prolongation and syncopes without deafmutism was first described by Romano[2] in a three month old girl suffering from syncopes for one month ECG's recorded during the attacks showed ventricular fibrillation, between the attacks, ECG findings consisted of prolonged QT variable T waves usually large and biphasic and short coupling ventricular premature beats Two of her brothers had died suddenly with the same symptoms at the age of 44 days and nine months respectively

In 1964 Ward[3] reported two new cases in two siblings a six year-old girl suffering from convulsions since the age of 16 months with ventricular fibrillation precipitated by exercise and documented by ECG recording her 17 month old

corded during hemodynamic studies performed three months later the results were in the normal range

The attacks The syncopes usually begin in early infancy or childhood Minor attacks with out loss of consciousness resemble hysterical or behavioral incidents When the patient is uncon scious the resemblance to epilepsy is obvious and the patient as in our case is treated with anticon vulsants they are usually induced by physical exertion or mental stress the simple ringing of an alarm clock provoked the attacks in one patient[14]

Their frequency decreases with increasing age[22] but deaths also occur in adulthood normaliza tion of the ECG with old age postulated to explain this improvement[21] was not seen in the family of our patient

The fainting attacks seem to have a later onset and be less frequent in the patients with small degrees of QT prolongation One of Fraser s pa tients who suffered from typical attacks in childhood had no further attacks for eight years and became a long distance runner at the age of 19, it seems therefore that some cardiac adapta tion takes place in early adulthood

Pregnancy seems to have a triggering effect on the attacks[23] menstruation induced the attacks in our patient and also in the patient of Ratshin and associates[11]

Incidence In view of the very small number of affected persons it is not easy to assess the fre quency of the gene

As regards Jervell and Lange Nielsen s syn drome Fraser Froggatt and Murphy estimate the prevalence to be between 1 6 and 6 per million population aged between 4 and 15 years in the British Isles

Studying the educational deafmutes they found less than 1 per cent of the syndrome (9 cases in 1 491 children) Sanchez Cascos and asso ciates[3] found one case in 511 children and James not a single case in 367 congenital deafmutes

Since deafness is usually not diagnosed in infancy and in view of the numerous cases of stillbirth or neonatal death with this genotype this tentative estimation is obviously too low

Romano Ward s syndrome is considered to be exceptional Since the attacks are usually mistak en for epileptic fits a correct diagnosis could be made with an ECG recorded at rest and after ex ercise in all children with a history of spells of unconsciousness

Prognosis The prognosis is very severe and in childhood mortality is high In a review, 10 cases of death between the ages of three and 14 years were found in 24 patients in Jervell and Lange Nielsen s syndrome[15]

In 12 cases of Romano Ward s syndrome col lected from the literature we found three deaths but obviously many cases of death among the siblings are not taken into account

Treatment A correct diagnosis is important not only for prognosis but because adequate treatment may be lifesaving and the patients can be spared long and ineffective anticonvulsant treatment. The treatment of choice is now pro pranolol [11,14] digitalis shortens the QT interval and normalizes the ECG in many instances its effect is however unpredictable diphenylhydan toin lidocaine diazepam calcium and glucose insulin potassium mixtures are usually ineffec tive although diphenylhydantoin shortens the QT interval in some cases [2,11] Potassium might give some good results in cases with hypokalem ia[7] and Jervell[2] succeeded in normalizing the ECG of a patient with a rapid infusion of potas sium chloride

Quinidine and procainamide prolong the repo larization and are contraindicated , adrenaline can induce ventricular fibrillation and must be banned in these patients[14]

Physical as well as mental stresses are to be avoided since the attacks are usually provoked by strenuous exercise or emotions Any surgical procedure even as trivial as a dental extraction must be carried out under continuous electrocar diographic monitoring

The anesthetic block of the left stellate gan glion was found to be effective while it was useless on the right side[1] left stellate ganglionec tomy was also successful the disease being possibly due to an imbalance between right and left sympathetic impulses

However Ratshin and associates[11] had no result with this treatment

Intracardiac pacing whose value has been questioned[2] might be the main treatment of recurring attacks[23]

Summary

A syndrome previously recognized by Romano and Ward is characterized by prolonged QT interval on the ECG and spells of unconscious ness

The case of a patient is reported with successive

Table II Electrocardiographic study

Subjects in Fig 6	RR (sec × 10⁻²)	Heart rate	QT Actual	QT Normal ± 0 04 sec	Comments	Syncopes
II 5	80	75	0 40	0 35	Diuretic treatment	–
II 6	66	92	0 34	0 32	Normal QT	–
II 9	84	72	0 46	0 36	Prolonged QT	–
III 4	68	88	0 36	0 32	Normal QT	–
III [illegible]	92	65	0 44	0 38	Slightly prolonged QT	–
III 7	106	56	0 51	0 40	Prolonged QT	–
III 8	72	82	0 36	0 34	Normal QT	–
III 9	104	58	0 40	0 40	Normal QT	–
IV 4	66	90	0 33	0 32	Normal QT	–
IV 7	56	110	0 36	0 29	Prolonged QT	+
IV [illegible]	92	65	0 44	0 38	Prolonged QT	+++
	80	75	0 44	0 35	Prolonged QT	
IV 11	68	88	0 36	0 32	Normal QT	–
V 4	50	120	0 28	0 27	Normal QT	–

Romano Ward's syndrome, without deafness is different, its inheritance is autosomal dominant with variable penetrance of the gene[1, 24, 25]

The family study of our patient points to the paternal grandfather as carrier of the gene, then the father himself The mother, unrelated to her husband, also has a moderately prolonged QT interval our patient might, therefore, be homozygous for this gene explaining the severity of her cardiac disturbances

Known heterozygous carriers have the same prolongation of the QT interval unassociated with clinical symptoms

It must be stressed, however, that accurate measurement of QT duration is uneasy due to the presence of a U wave and that the QT interval varies with numerous factors sex, age heart rate calcium or potassium blood levels various drugs, such as digitalis diuretics quinidine and phenothiazine derivatives angina, and myocarditis cerebrovascular disease may also be responsible for this prolongation[38]

But none of these factors seemed to be involved in the parents of our patient

It is not clear at the present time whether in the families hitherto described one is dealing with the same mutation as the phenotypic expression is quite variable within and between families

Pathogenesis of cardiac disturbances The mechanism of ECG changes and ventricular fibrillation in this syndrome is not clear

Fraser and co workers[7, 9] demonstrated at the autopsy of two cases cardiac conductive system changes Purkinje fibers sparse and atypical, Mathews, Blount, and Townsend[2] also found in one autopsied case fibrosis in the conductive system, these changes should induce an abnormal depolarization[32] and probably no modification of repolarization, but human Purkinje system anatomy and function are still imprecise, and its responsibility in this syndrome remains obscure

Ischemia of sinusal node by an hereditary abnormality of small coronary vessels has also been postulated[7] Other hypotheses are asymmetrical stimulation of ventricular muscle[39] lack of synchronism in ventricular muscle refractory period,[40] and myocardial hypersensitivity to catecholamines[9] since sympathetic stimulation sometimes prolongs the QT interval[39]

A cardiac metabolic error with or without lack of a specific enzyme is more likely[1, 6, 41]

Jervell[4] assumes that a retention of potassium in the myocardial cell could be the basic mechanism, inducing a decrease in ATPase activity and a reduced effectiveness of the sodium pump it must be stressed, however that erythrocyte membrane ATPase activity assessed in three patients was found to be normal[42]

The absence of perinuclear clear zone containing glycogen in the Purkinje fibers, and the normal mechanical systole with delay in repolarization and increased duration of electrical systole seem to point to a disturbed myocardial metabolism[9]

The rare hemodynamic angiographic studies gave normal results[21, 32, 34] except for a strong tendency to ventricular arrhythmia[10]

In our patient, there was no arrhythmia re

corded during hemodynamic studies performed three months later the results were in the normal range

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Summary

A syndrome previously recognized by Romano and Ward is characterized by prolonged QT interval on the ECG and spells of unconsciousness

The case of a patient is reported with successive

ECG recordings during the attacks, ventricular flutter and multifocal ventricular tachycardia were noted, with rapid spontaneous recovery and relapse

Cases of stillbirth and sudden death in infancy among the siblings together with QT interval prolongation in the relatives point to an autosomal dominant transmission with the propositus being apparently homozygous The chromosomes of the patient are normal

The attacks were controlled by the association of propranolol and digitalis which seems to be the optimal long term therapy in such cases

In view of the poor prognosis in untreated cases, and the good results of a correct therapy, an ECG should be recorded at rest and after exercise in all children suffering from spells of unconsciousness

Addendum

Ward (cited by Singh and Hausworth[46]) considers that carbamazepine might be the best antiarrhythmia drug in this syndrome

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Cardiomyopathy associated with amphetamine administration

H J Smith M B, M R A C P
A H G Roche, M B, M R A C P
M F Jagusch M B F R C P A
P B Herdson, M B, B Med Sc Ph D, F R C P A
Auckland New Zealand

There is a great deal of experimental evidence which suggests that catecholamines especially isoproterenol, may induce myocardial necrosis in animals when administered acutely in large doses[1-4] Recently, extension of the size of myocardial infarctions following coronary artery occlusion in anesthetized animals has also been reported to occur with isoproterenol,[5] and myocardial hypertrophy has been produced by chronic infusion of subhypertensive doses of nor epinephrine in the dog There have however, been no convincing reports in the literature to suggest that chronic ingestion of sympathomimetic amines by patients may lead to clinical heart disease We report a case of cardiomyopathy in a patient receiving long term dextroamphetamine in whom there appears to be a causal relationship between the cardiomyopathy and amphetamine ingestion

Case report

A 4? year old woman was referred for the management of severe congestive heart failure in July 1971

Twelve years previously in 1959 she became unwell with a depressive illness which was treated with dextroamphetamine In the subsequent five years a variety of antidepressant drugs was used and she underwent a course of electroconvulsive therapy The initial course of dextroamphetamine was continued intermittently

In 1964 after intensive psychiatric and neurologic investigation the diagnosis of narcolepsy with cataplexy was made and she was commenced on high dose dextroamphetamine at 25 mg four times a day

In 1965 she developed ankle edema which progressed with increasing shortness of breath and orthopnea but later responded to treatment

In 1968 she was found to have gross bilateral ankle edema iron-deficient anemia and mildly deranged liver function tests She was treated with ethacrynic acid frusemide triamterene and prednisone with some reduction of her ankle edema Dextroamphetamine therapy was continued without interruption

By 1969 she had frank congestive cardiac failure with pleural effusions ascites and gross edema involving legs sacrum and lower chest She was severely limited by dyspnea and spent most of her day in a chair She refused hospital treatment and continued to take dextroamphetamine In March 1970 an attempt was made to withdraw dextroamphetamine but replacement with methylphenidate (Ritalin) was unsuccessful Her admission in July 1971 was precipitated by increasing shortness of breath and ischemia of the toes associated with severe ankle edema A femoral arteriogram showed no evidence of peripheral vascular disease Her congestive heart failure had been unresponsive to frusemide 160 mg per day spironolactone 200 mg per day and digoxin 0 25 mg per day She continued to take dextroamphetamine 100 mg per day

Physical examination (July 1971) showed a cachexic depressed middle aged woman She had a pulse rate of 100 per minute in sinus rhythm with a blood pressure of 120/80 mm Hg She was not dyspneic at rest but the jugular venous pressure was at 2 cm above the sternal angle The heart was enlarged almost to the anterior axillary line in the fifth intercostal space and auscultation revealed a soft pansystolic murmur at the cardiac apex with a prominent third heart sound The liver was just palpable below the costal margin and she had bilateral leg edema with ischemic changes in the toes Peripheral pulses were obscured by the presence of edema There was generalized muscle wasting consistent with prolonged bed rest and no fasciculation was present The peripheral nervous system was normal

The electrocardiogram (Fig 1) showed sinus rhythm at a rate of 100 per minute with p mitrale and left bundle branch block The chest x ray (Fig 2) showed the heart to be enlarged with a cardiothoracic ratio of 0.?7 The lateral view suggested

From the Department of Cardiology Green Lane Hospital and the Department of Pathology Medical School Auckland New Zealand

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Reprint requests Dr A H G Roche Cardiology Department Green Lane Hospital Auckland New Zealand

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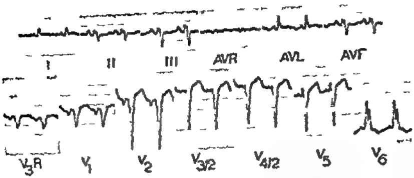

Fig 1 Electrocardiogram taken in July 1971 shows left bundle branch block and left atrial strain

Table I Results of cardiac catheterization

Cardiac index	2 5 L./min /M
Heart rate	105 beats/min
Stroke volume index	62 mL/beat/M
Pressures	
Pulmonary artery wedge	A = 45 V = 50 (4?)†
Pulmonary artery	80/42 (60)
Right ventricle	82/22
Right atrium	A = 24 V = 18 (18)
Left ventricle	145/55
Ascending aorta	150/95 (120)
Pulmonary arteriolar resistance index	65 units M
Systemic resistance index	43 units M

All pressures recorded with mid-chest zero reference
†Mean pressures in parentheses.

that the cardiomegaly was mostly left ventricular The pulmonary veins in the upper zones were prominent and initially pulmonary edema with pleural effusions was present The following laboratory investigations were normal hemoglobin white cell count erythrocyte sedimentation rate glucose electrolytes creatinine calcium, phosphorus cholesterol uric acid protein electrophoresis bilirubin and alkaline phosphatase The serum urea was 49 mg per 100 ml and the SGOT was 70 MIU per milliliter (normal, 10 to 50 MIU per milliliter)

Cardiac catheterization was performed on Dec 7 19 1 and the findings are summarized in Table I The results confirmed the clinical impression of biventricular heart failure however the etiologic basis for the failure could not be established In particular there was no evidence of pericardial constriction valve disease or intracardiac shunt Mild systemic hypertension (central aortic pressure 150/95 mean 120 mm Hg) was felt to be an inadequate basis for her incapacitating heart failure Selective coronary angiography revealed no significant stenotic lesion of either coronary system Left ventricular cineangiogram showed a generalized reduction in myocardial contractility with a markedly enlarged left ventricle and large end systolic volume There was no evidence of localized hypokinesis or aneurysm formation

A diagnosis of cardiomyopathy of uncertain etiology was made however in view of the chronic intake of large doses of dextroamphetamines over a long period of time the possibility

Fig 2 Chest x ray taken in July 19?1 showing cardiomegaly and pulmonary venous congestion

of this sympathomimetic amine being responsible for the cardiomyopathy became a serious consideration

A program of amphetamine withdrawal was therefore attempted in the knowledge that her mental state might deteriorate but it was felt that the benefit accruing from improved cardiac performance might outweigh the disadvantages of relapse of her psychiatric condition

Dextroamphetamine 100 mg per day was therefore reduced to 60 mg per day and then to 30 mg. per day in divided doses. Predictably she became extremely depressed and very drowsy Her cardiac status deteriorated with increased fluid retention and severe dyspnea Frusemide was increased to 240 mg. per day and digoxin spironolactone and supplementary potassium were continued but no response was obtained It seemed likely that she had developed a physical cardiac dependence on dextroamphetamine The amphetamine withdrawal program was abandoned in favor of conservative nursing care

Following the re introduction of dextroamphetamine at 100 mg per day her cardiac status improved somewhat with the

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disappearance of some of her peripheral edema She was eventually discharged home in partially compensated heart failure but she died approximately 10 weeks later

Autopsy

Abnormal findings at autopsy were limited to the cardiovascular system In particular there were no demonstrable lesions in the brain system

Gross The heart was enlarged (530 Grams) and rather floppy with dilation of all chambers in the left ventricle The coronary arteries were widely patent and strikingly free of atheroma The heart valves were normal and there was no evidence of abnormal intracardiac communication The ventricular walls were of normal thickness but showed grey white foci of fibrosis throughout the musculature particularly in the left ventricle Areas of adherent mural thrombus were present in the right atrial and both ventricular chambers

Light microscopy Systematic histologic examination of the heart was undertaken with sections from all four chambers Similar changes were present in all sections examined but were most marked in the left ventricular myocardium (Fig 3) Widespread interstitial edema with a scattered predominantly lymphocytic and histiocytic cellular infiltrate was present between muscle fibers Individual muscle fiber degeneration with small areas of muscle necrosis was present and about these areas the cellular infiltrate tended to be more prominent with scattered cells having the appearance of Anitschkow myocytes

Patchy fibrosis was apparent (Fig 3) ranging from small dense hyaline areas to areas which were more cellular with fibroblastic activity scattered inflammatory cells and evidence of vascularization No evidence of amyloidosis sarcoidosis or other infiltrative disorders was found and there were no signs of vasculitis

Electron microscopy Electron microscopy revealed widespread abnormalities of the myocardial fibers with extensive margination of nuclear chromatin marked interfibrillar edema and severe mitochondrial abnormalities The mitochondrial abnormalities included loss of matrix together with the presence of large intramitochondrial granules in virtually all the mitochondrial sections Some myofibrils showed apparent rupture close to the Z bands and there were a number of lipid droplets in various parts of most cells (Fig 4)

Discussion

The acute administration of massive doses of catecholamines is known to produce widespread myocardial infarction in experimental animals Kahn Rona and Chappell[1] and Zbinden and Moe[2] have shown this with isoproterenol while Halpern Morard and Drudi Baracco[3] have demonstrated a similar phenomenon with amphetamine Laks Morady and Swan infused subhypertensive doses of norepinephrine into dogs for periods of six to 63 weeks and demonstrated production of myocardial hypertrophy

We have not found any report of the effects of chronic administration of catecholamines to patients For example cardiac failure has not been reported in amphetamine addicts While many such addicts are taking 30 to 60 mg per day there are some who undoubtedly exceed the dose range taken by our patient On the other hand amphetamine rarely represents the end stage of the spectrum of drug addiction as many amphetamine addicts move on to narcotics or other drugs Our patient was treated with a dose of 100 mg per day (approximately 2 mg per kilogram per day) intermittently for five years and continuously for seven years

We believe that chronic exposure to high doses of amphetamine probably produced her cardiomyopathy resulting in dependence on the drug One may speculate that the enhanced sympathetic drive of amphetamine led to an insidious biochemical exhaustion which resulted in cardiomyopathy Alternatively the cardiomyopathy may be the end result of chronic myocardial hypertrophy induced by dextroamphetamine Evidence from two clinical conditions can be cited in support of the possibility that ingestion may lead to the development of cardiomyopathy

Many years ago both Hausmann and Getzowa[7] and Bieble and Wiechels described the association of myocardial fibrosis and adrenal tumors which may have been pheochromocytomas Later Raab[9] showed that myocardial lesions and ventricular hypertrophy may occur with pheochromocytoma More recently myocarditis occurring in associations with pheochromocytoma was described by Kline[1] Subsequently,

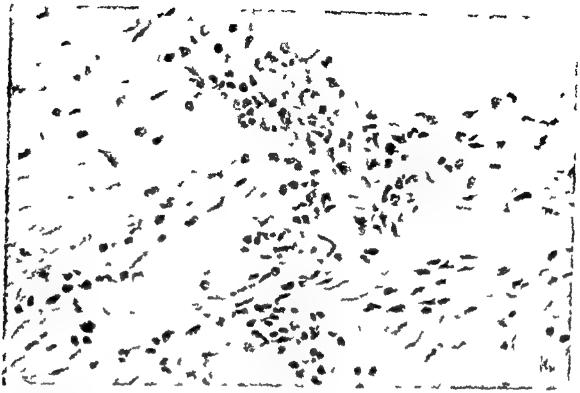

Fig 3 Light microscopic section of a focus of myocardial fiber degeneration and cellular infiltrate Lateral right ventricular wall (× 1 100)

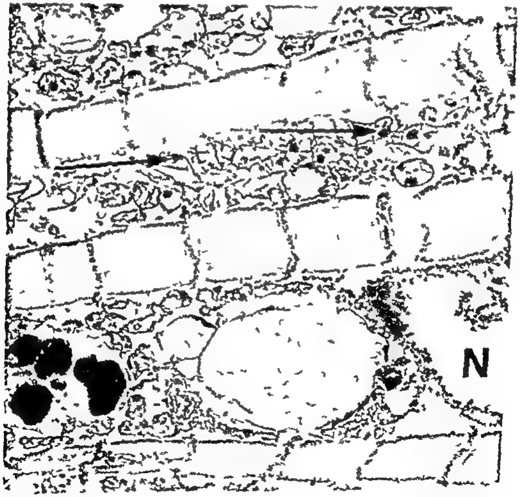

Fig 4 Electron microscopy The nucleus (N) shows margination of chromatin Prominent intramitochondrial granules (→) with marked interfibrillar edema are present (× 10 000)

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Van Vliet, Burchell, and Titus[11] in a series of 26 patients with pheochromocytoma found myocarditis in 15 (58 per cent) patients at autopsy The excessive catecholamine secretion in patients with pheochromocytoma may be regarded as a continual endogenous administration of catecholamines, a situation analogous to that seen in our patient Van Vliet, Burchell, and Titus[11] described focal degeneration and necrosis of myocardial cells Diffuse edema of the myocardium was present, and lesions were present in all four chambers although most pronounced in the left ventricle They also described an increase in fibrous tissue closely associated with the areas of degeneration

In thyrotoxicosis thyroxin appears to affect the heart directly as well as indirectly[11] The level of catecholamine in the heart in thyrotoxicosis is increased There is also an enhanced sensitivity of the myocardium to the effect of circulating catecholamines This is mediated through the action of thyroid hormone on the cyclic adenosine monophosphate/adenyl cyclase system The status of thyrotoxic cardiomyopathy as a distinct pathologic entity however is much less secure In a few instances, where autopsy findings have been documented[12] intracellular myofibril lipid changes, together with interstitial myocarditis have been described but the changes described are much less than those seen in pheochromocytoma

There is doubt as to the reversibility of myocardial lesions produced by catecholamines although a case of reversible myocarditis with pheochromocytoma reported by Engelman and Sjoerdsma[14] raises this possibility The situation with thyrotoxic cardiomyopathy is even less certain Our patient presented at a terminal stage and withdrawal of amphetamine did not reverse or improve the cardiac abnormalities However it is possible that the changes would have been reversible if amphetamine had been withdrawn at an earlier stage

It is of interest that Citron and co workers[15] described an arteritis in patients on amphetamine, but we found no evidence of this in our patient at autopsy

Conclusion

We report a patient with cardiomyopathy presenting with congestive heart failure in the absence of coronary heart disease valve lesions or other demonstrable cause The history of chronic ingestion of dextroamphetamine in high doses together with the histologic similarity to myocarditis of pheochromocytoma raises the possibility that the drug may have been responsible for the cardiomyopathy

Summary

A 45 year old woman with congestive heart failure, in whom there was no evidence of coronary heart disease, valve disease, or other demonstrable cause of heart failure, was found to have taken high doses of dextroamphetamine over a long period Withdrawal of amphetamine resulted in deterioration, suggesting a physical cardiac dependence on the drug The clinical and autopsy findings are presented and the similarities to the myocarditis associated with pheochromocytoma are discussed The evidence presented suggests a causal relationship between administration of dextroamphetamine and the cardiomyopathy

We wish to thank Dr J B Lowe Dr D M Hanna and Dr C T Jones under whose care the patient came at various times, for permission to publish

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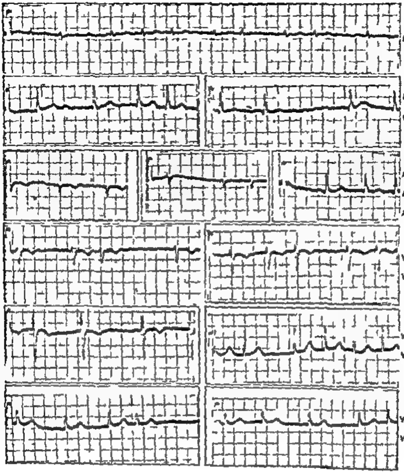

Fig 2 FCG taken on Aug 16 1973 the day of death showing atrial fibrillation with a ventricular response of 60 per minute

time the cardiac examination revealed a systolic ejection murmur but was otherwise unremarkable The patient continued to do well and returned for a routine hospital visit on Aug 23 1972 and was found again to be in atrial fibrillation with a heart rate of 60 per minute Cardiac examination at that time described a Grade 2/4 diastolic rumble heard best with the patient in the left lateral decubitus position In addition a third heart sound was heard which was described as an opening snap The patient was referred to the cardiac clinic with the diagnosis of possible rheumatic heart disease Chest roentgenogram at this time was again essentially negative The patient was seen 2 months later in the cardiac clinic where a physical examination was completely normal and no murmurs could be heard by several cardiologists In March 1973 the patient had another episode of dyspnea and she was found to be in normal sinus rhythm with PR interval of 0 24 A chest roentgenogram at that time showed some mild venous congestion but no frank pulmonary edema The patient returned a week later for a routine visit and was asymptomatic In June 1973 the patient was seen in the hospital and for the first time since August 1972 the diastolic rumble was heard along with an augmented first heart sound No opening snap or third heart sound was heard during this visit The clinical impression at the time was that the patient probably had mild rheumatic mitral stenosis and because of her age no further studies were indicated

The final episode began on Aug 16 1973 when syncopal attacks occurring earlier that day brought the patient to the hospital emergency room where she experienced no further symptoms On admission her blood pressure was

Clinical pathologic conference

"Hole-in-one" sudden death Mitral stenosis and left atrial ball thrombus

J T Lie M D F A C C
M L Entman, M D, F A C C*
Houston Texas

Case presentation

An 83 year old woman was brought to the hospital on Aug 16 1973, by her daughter, after having "passed out three times on the day of admission The daughter related that each of the syncopal episodes was sudden in onset and lasted only a few seconds and that the patient had no seizure activity although she was incontinent of urine

The patient had been reasonably well all her life She had a vague history of hypertension treated intermittently with Reserpine In addition diabetes mellitus had been previously diagnosed and she had been taking oral hypoglycemic agents since the age of 75 She had complained of occasional episodes of exertional chest pain that were relieved by nitroglycerin and several years previously mild symptoms of congestive heart failure Despite this the patient did not consider herself to be limited in her physical activity on a routine daily basis In 1970 the patient had an episode of transient aphasia, right hemiparesis and right hemiparesthesia but recovered completely from these within a short period of time She was found to be in atrial fibrillation with a slow ventricular response and was started on a maintenance regime of digoxin, 0 125 mg daily in addition to oral hypoglycemic drugs and Reserpine

From the Departments of Pathology and Medicine (Cardiology) Baylor College of Medicine and Ben Taub General Hospital Texas Medical Center Houston, Texas

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Reprint requests J T Lie M D., Department of Pathology Baylor College of Medicine 1200 Moursund Houston Texas 77025

*Howard Hughes Medical Investigator

Fig 1 Chest roentgenogram taken on Feb 27 1972 some 18 months before death showing slight cardiomegaly and interstitial pulmonary edema

She was next seen on Feb 22 1972 complaining of mild dyspnea on exertion and a cough Physical examination revealed wheezing and rales in the lungs but no elevation in jugular venous pressure Cardiac examination was negative Chest roentgenogram showed mild cardiomegaly and interstitial pulmonary *edema (Fig 1) and the* electrocardiogram (ECG) showed slow atrial fibrillation as before On routine follow up a month later the patient's chest roentgenogram was clear and she was asymptomatic At that

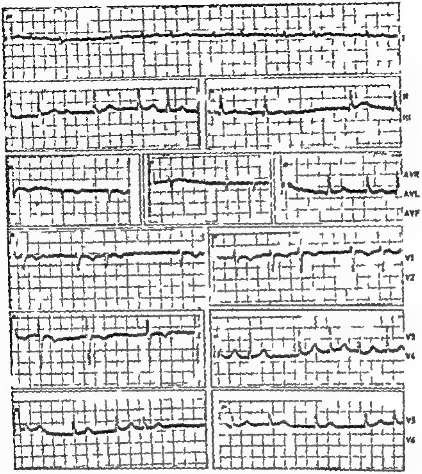

Fig 2. ECG taken on Aug 16 1973 the day of death, showing atrial fibrillation with a ventricular response of 80 per minute

time the cardiac examination revealed a systolic ejection murmur but was otherwise unremarkable The patient continued to do well and returned for a routine hospital visit on Aug 23 1972 and was found again to be in atrial fibrillation with a heart rate of 60 per minute Cardiac examination at that time described a Grade 2/4 diastolic rumble heard best with the patient in the left lateral decubitus position In addition a third heart sound was heard which was described as an opening snap The patient was referred to the cardiac clinic with the diagnosis of possible rheumatic heart disease Chest roentgenogram at this time was again essentially negative The patient was seen 2 months later in the cardiac clinic where a physical examination was completely normal and no murmurs could be heard by several cardiologists In March 1973 the patient had another episode of dyspnea and she was found to be in normal sinus rhythm with PR interval of 0 24 A chest roentgenogram at that time showed some mild venous congestion but no frank pulmonary edema The patient returned a week later for a routine visit and was asymptomatic In June 1973 the patient was seen in the hospital and for the first time since August 1972 the diastolic rumble was heard along with an augmented first heart sound No opening snap or third heart sound was heard during this visit The clinical impression at the time was that the patient probably had mild rheumatic mitral stenosis and because of her age no further studies were indicated.

The final episode began on Aug 16 1973 when syncopal attacks occurring earlier that day brought the patient to the hospital emergency room where she experienced no further symptoms On admission her blood pressure was

140/100 mm Hg and she had a pulse rate of 90 per minute. However, some time during the course of her time in the emergency room, a peripheral pulse of 32 per minute was noted. Serum electrolytes were normal and the ECG revealed atrial fibrillation with a ventricular response of 80 per minute (Fig 2). The patient claimed that she felt perfectly well and was instructed to stop taking digoxin for 2 days and to return to the hospital for a follow up evaluation. When she was about to enter her car in the hospital parking lot, she experienced another sudden syncopal episode and was taken back to the hospital as she was recovering. By the time she arrived in the emergency room, however, she was comatose and found to be in cardiorespiratory arrest with no peripheral pulses. An ECG showed narrow QRS complexes at 20 per minute, and cardiopulmonary resuscitation was applied. Thirty minutes later, the ECG had become virtually a flat line, and she was cyanotic. Spontaneous respirations were weak and intermittent, and the pupils were fixed in the mid position. Jugular venous pulse was fully distended and the heart rate varied from 100 to 150 beats per minute. She died shortly thereafter.

Clinical discussion

DR M L ENTMAN: This is the story of a woman who was found to have the late onset of a diastolic rumble diagnosed as probably of rheumatic origin. It would be extremely unusual for a woman to remain asymptomatic from mitral stenosis until her 80s and not have signs of left atrial enlargement, a past history of congestive heart failure, or a past history of rheumatic heart disease. It has been estimated that the average time between the onset of rheumatic heart disease and the onset of symptomatic mitral stenosis is 20 to 30 years[1] which would place this lady's episode of rheumatic fever (if there were such an episode) in her sixth decade. Although all things are possible, we must therefore consider the possibility that the diastolic murmur in this case emanated from a cause other than mitral stenosis.

Perhaps the most common problem to mimic mitral stenosis is a left atrial mass obstructing the inflow tract, such as a left atrial myxoma or atrial thrombi. Factors which suggest that a diastolic rumble may be emanating from a left atrial mass are (1) a history of syncope—syncope is rare in mitral stenosis, (2) positional changes in symptoms or signs, (3) intermittent symptoms or signs, (4) poor symptom sign correlation—a patient with no symptoms may be found to have an S3 heart sound mimicking an opening snap which occurs very close to the second heart sound, (5) radiographic finding of normal left atrial size and normal pulmonary vasculature in a patient with a long standing diastolic murmur, (6) advanced age at onset of symptoms in a patient without a previous history of rheumatic fever or rheumatic heart disease, and (7) history of peripheral embolism as a presenting complaint in a previously asymptomatic patient. It is also possible, however, that a left atrial mass (particularly in the case of left atrial thrombi) and mitral stenosis may occur simultaneously.

It is clear that a number of the factors mentioned above were present in this patient's history. She presented with syncope, had intermittently heard diastolic murmurs and third heart sounds, did not have true symptoms until the age of 80, and had a history of a cerebral ischemic episode from which she recovered extremely rapidly, suggesting the possibility that the episode emanated from a cerebral embolus. In addition, her pulmonary vasculature was normal and did not suggest mitral stenosis, and she had a normal sized left atrium.

The patient's ECG was normal with the exception of the atrial fibrillation and the one episode of normal sinus rhythm demonstrated normal size P waves with a prolonged PR interval. This leads us to consider the possibility that the patient had a left atrial mass, and the most likely cause of a left atrial mass would be a left atrial myxoma. The age distribution of left atrial myxomae has not been extensively documented in the literature. In personal communications with Dr John Fenoglio of the Armed Forces Institute of Pathology (AFIP), I have been assured that there is no selective age distribution and that atrial myxomas have been discovered in people in their 80s. Characteristic of patients above 60 years old with atrial myxoma was that the tumors were often missed clinically during life. Of interest, the most common symptoms were congestive heart failure and syncope. Emboli were also quite frequent with cerebral emboli being the most common. Very few of the

Fig 3 Dilated and thick walled left atrium with the spherical ball thrombus lifted out from the bottom of the cup to show a stenotic mitral valve with "fish mouth" deformity

patients in the AFIP series died a sudden death but sudden death has been reported in the past by others It is also of interest that atrial myxomas need not have catastrophic clinical courses and a report in the literature of a patient followed for 43 years who was found to have an atrial myxoma was reported before the advent of surgical therapy for this My preliminary clinical diagnosis is therefore *a left atrial mass probably a left atrial myxoma producing inflow tract obstruction to the left ventricle*

The next question is what was the terminal episode and this is also difficult to assess At the time when the patient was observed to have a pulse of 32 per minute despite the fact that her ECG showed a ventricular rate of 80 or more per minute the patient was alert cooperative and in no apparent distress This suggests that the more obvious conclusion of inflow tract obstruction may be over simplified It would seem that were the mitral valve being occluded sufficiently so that only 32 palpable pulses could occur out of 80 ventricular contractions per minute there would be marked elevation of left atrial pressure and the patient would be short of breath The question also arises as to why did this woman die suddenly rather than just have a syncopal episode as she had previously during that day If a pedunculated left atrial myxoma were intermittently occluding the inflow tract to cause syncope what changed this fourth and final episode so that it resulted in death One possibility is that the mass became dislodged from the left atrial wall and had totally occluded the circulation This has been reported in the past as a cause of death in myxoma [1] The question then arises as to where did the tumor become lodged The two possibilities are that (1) the tumor became lodged in the mitral ring and in that case the reported pulse deficit would be difficult to explain or (2) the tumor had entered into the left ventricle where it occluded the outflow tract Physical examination before the patient s death demonstrated a systolic ejection type of murmur and complete absence of previously heard diastolic murmur It could be postulated therefore that the left atrial mass became dislodged from the left atrium and descended into the left ventricle where it partially occluded and later completely occluded the left ventricular outflow tract Such an obstructive tumor could explain the pulse deficit observed without requiring as high an elevation of the left atrial pressure The reason for the mass not being ejected from the ventricle could result either from

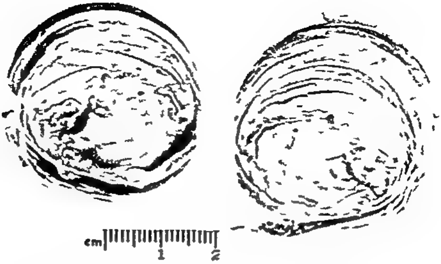

Fig 4 Bisected ball thrombus showing the internal laminated structure

the size of the mass or rigidity of the aortic valve which was hemodynamically insignificant until the present episode

Clinical diagnoses

1 *Left atrial mass* producing a diastolic murmur and syncope with intermittent episodes of congestive heart failure *probably a left atrial myxoma*

2 Dislodged left atrial mass occluding the systemic circulation causing sudden death

Pathologic findings

Dr J T Lie Autopsy showed that the patient had died with acute pulmonary congestion and edema She had bilateral bloody hydrothorax approximately 200 ml in each pleural cavity Although the combined lung weight mass was 1 180 grams microscopically there were diffuse engorgement of the alveolar capillaries and marked distention of the air spaces with proteinaceous fluid In addition the lungs showed mild fibrosis of the alveolar septa and mild to moderate intimal thickening of the pulmonary arterioles

The pericardium contained 75 ml of clear fluid The heart weighed 450 grams A large spherical mass was palpable moving freely within the dilated and thick walled left atrial cavity On incising the left atrium, it was immediately apparent that a ball thrombus 3 8 cm in diameter had become separated from its attachment to the septal wall of the left atrium and lodged snugly over the mitral opening completely obstructing it (Fig 3) The mitral valve was both stenotic and incompetent and showed the fish mouth deformity produced by fusions of the commissures and fibrous thickening of the valve leaflets The ball thrombus completely spherical had a smooth external surface and on sectioning was shown to be composed entirely of old laminated thrombotic material (Fig 4)

The microscopic sections of the atrial and ventricular myocardium showed endocardial thickening and multifocal interstitial fibrosis but no Aschoff's nodules There was only mild to moderate coronary atherosclerosis Apart from moderate generalized visceral congestion the only other significant finding was histologic evidence of cerebral microinfarcts involving the basal ganglia and hippocampus

Anatomical diagnoses

1 Cardiomegaly with moderately severe mitral stenosis and incompetence presumably of rheumatic origin
2 Detached ball thrombus of the left atrium completely obstructing the mitral opening
3 *Acute pulmonary edema and generalized* visceral congestion
4 Pleural and pericardial effusions
5 Old cerebral microinfarcts

General comment

Dr Lie Sudden death in this octogenarian woman was brought about by the most unusual occurrence of impaction of the mitral valve by a large ball thrombus The ball thrombus had

apparently become detached either spontaneously or incidental to the final resuscitative efforts, and rolled down the cup of the left atrial cavity to block off the mitral opening completely Thus metaphorically speaking we were witnessing a hole in one type of situation and the outcome was just as dramatic and definitively final as it would be on the eighteenth green Incidentally the size of the ball thrombus was almost identical to that of a standard sized golf ball

The term ball thrombus was introduced by Wood who reported the first case of left atrial ball thrombus in 1814 He described a 15 year old girl whose chief complaint was fainting spells occurring three or four times a day Clinical suspicion of mitral stenosis was confirmed at autopsy and a spherical thrombus 1½ inches in diameter was also found within the left atrium Macleod[7] 69 years later described the first case of right atrial ball thrombus

Although antemortem thrombus in the atria (especially atrial appendages) is not unusual in a variety of heart diseases massive left atrial thrombi are uncommon without mitral valve disease and atrial fibrillation Ball thrombi are exceedingly rare Read and colleagues were the last to have searched the literature and found about 60 reported cases The autopsy incidence of ball thrombi is about one in 2 000 to 3 000 An atrial thrombus to be designed as ball thrombus must meet the rigid criteria as enunciated by Welch in 1899 that there should be (1) entire absence of attachment and consequent free mobility (2) imprisonment in consequence of excess in the diameter of the thrombus over that of the first narrowing in the circulatory passage ahead of it and (3) such consistence and shape that the thrombus must not of necessity lodge as an embolus in this passage The third point does not prejudice the question of the possibility of a ball thrombus lodging as an embolus but it excludes from the group detached shaggy irregular masses as must necessarily be caught at once as emboli in the narrow passage in front It is possible that the apparent rarity of ball thrombi (as recorded in the literature) is due in part to the restrictive criteria of Welch[12]

Garvin considered the distinction between pedunculated and free ball thrombus to be entirely academic since both could produce the same symptoms Evans and Benson[1] suggested abandoning the term ball thrombus in favor of the more general designation mass thrombus for any thrombus free or attached occupying most of the left atrium or for any smaller thrombus that could obstruct the mitral valve

Antemortem diagnosis of (right or left) atrial ball thrombus is certainly possible though it would call for a high index of clinical suspicion The criteria laid down by Battistini[11] in 1909 still apply signs of mitral stenosis changing murmurs disturbance of the general circulation postural variations of the pulse and gangrene of the lower extremities In addition Evans and Benson[1] and Abramson emphasized the frequency of hemiplegia that might be transient in nature

As noted before the first patient that of a 15 year old girl described by Wood[6] was the youngest known and the oldest was probably the 86 year old woman reported by Garvin[10] The peak age incidence among the reported cases was in the fifth decade with a 3 1 female sex predilection Although mitral stenosis and atrial fibrillation were present in the majority of patients they are by no means the absolute prerequisites A ball thrombus has also been described as a complication of infective endocarditis It should also be pointed out that the clinical findings of an atrial ball thrombus and myxoma are similar and both are amendable to surgery in averting the threats of embolic complications and sudden death

We thank Ms Fran Skinner CT (ASCP) HT, for the excellent gross photography of Figs 3 and 4

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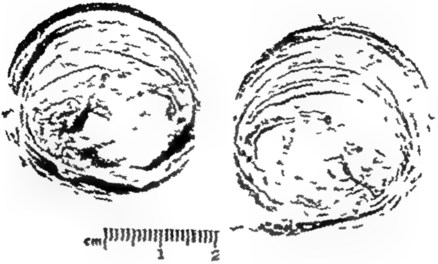

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Clinical uses of His bundle electrocardiography Part III

Masood Akhtar M D
Anthony N Damato M D
Sun H Lau M D
Andres R Ticzon M D
Staten Island N Y

Wolff Parkinson White (WPW) syndrome

Both His bundle and epicardial mapping techniques[2,3] have significantly helped in clarifying some aspects of the WPW syndrome In addition these studies have given further testimony to the myriad complexities involved in this syndrome Pre excitation of the ventricles resulting in a delta wave and short P R interval (p to delta) constitute the basic electrocardiographic (ECG) abnormality and the hallmark for recognition of this syndrome[4] During sinus rhythm ventricular pre excitation may always be present or may alternate for varying periods of time with normal ventricular activation The frequent occurrence of supraventricular tachycardias (mostly re-entrant in nature) in patients with pre excitation make this syndrome an important clinical entity There exists considerable anatomic and electrophysiologic evidence indicating that the delta wave represents early activation of the ventricles by an atrial impulse which is antegradely conducted to the ventricles via a bypass or anomalous tract (bundle of Kent) Since atrial impulses are simultaneously conducted to the ventricles through the normal A V pathway the QRS complex in a majority of cases represents fusion activation i e the delta wave represents ventricular pre excitation through the bypass tract and the rest of the QRS complex is due to activation of the ventricles through the normal A V nodal HPS Thus most patients with the WPW syndrome will demonstrate a normal A H interval and a foreshortened H V interval (Fig 1 panel *A*) If an atrial impulse is significantly delayed or blocked within the A V nodal His Purkinje System (HPS) the ventricles will be totally activated via the bypass tract Conversely if A V nodal conduction is enhanced a greater amount of ventricular excitation will occur through the normal A V conducting system and the QRS complex will tend toward normalization

Total pre-excitation of the ventricles can be achieved either by incremental atrial pacing or by premature depolarization of the atrium during the refractory period of the A V node Incremental atrial pacing causes progressive delay or block within the A V node while the P to-delta interval usually remains constant As a result of the increasing A H intervals the bundle of His deflection merges into and is obscured by the ventricular electrogram (Fig 1 panel *A*)

Fig 1 shows the effect of premature atrial depolarizations The P to delta interval remains constant but there is progressive A V nodal delay The premature atrial beat in panel *B* reaches the bundle of His after the ventricles have been totally pre-excited by the anomalous pathway If A V nodal delay is significant and the ventricular muscle has recovered double excitation of the ventricles by a single atrial impulse will occur (panel *C*)

Pre-excitation can mimic the ECG pattern of myocardial infarction[7,8] The distinction can be made by 'normalizing' the QRS complex which can almost always be achieved by introducing a premature atrial depolarization during the effective refractory period of the accessory pathway When the ventricles are activated entirely by the

From the Cardiopulmonary Laboratory United States Public Health Service Hospital, Staten Island New York.

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Reprint requests Masood Akhtar M D Cardiopulmonary Laboratory United States Public Health Service Hospital Staten Island, N Y 10304

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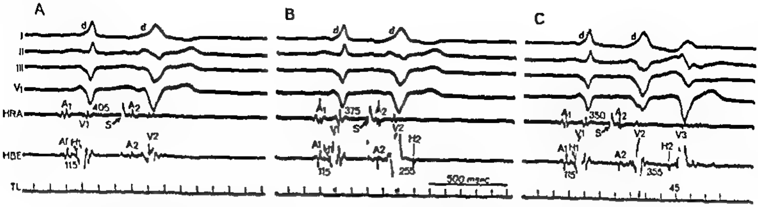

Fig 1 Effect of atrial premature stimulation in ventricular pre excitation The first beat in panel *A* is a sinus beat The A H interval measures 115 msec and the H V interval (H delta) is nonexistent The orientation of delta on the surface ECG is suggestive of type A ventricular pre excitation A premature atrial beat (A_2) results in delay in A V nodal conduction time such that H_2 merges into and is obscured by the ventricular electrogram The P to delta interval remains constant and the QRS shows more pre excitation compared to the preceding sinus beat In panel *B* an earlier premature beat results in further increase in A H interval and H_2 now emerges from the ventricular electrogram Ventricular activation occurred exclusively via the bypass tract since no contribution to ventricular activation can be expected from the premature impulse traveling along the normal pathway Panel *C* demonstrates double ventricular activation from a single premature atrial beat resulting first from exclusive conduction over the bypass tract and second by conduction along the normal pathway

A V nodal His Purkinje system the resultant QRS pattern can be examined for the presence or absence of changes consistent with infarction or ischemia (Fig 2)

The incidence of supraventricular tachycardias (SVT) in patients with the WPW syndrome has been estimated to be as high as 70 per cent and an overwhelming number of these are re entrant in nature[9-11] However patients with this syndrome may also develop ectopic atrial tachycardias or atrial fibrillation During atrial fibrillation antegrade conduction may occur along the A V node HPS or accessory pathway (Fig 3) The latter may mimic or induce ventricular tachycardia and fibrillation

Re entrant tachycardias are most often initiated by premature atrial beats (Fig 2 panels *D* and *E*) and less commonly by ventricular extrasystoles Since the majority of re entrant tachycardias are associated with normal QRS complexes it is generally accepted that the reciprocating impulse is antegradely conducted to the ventricles by the A V nodal HPS and retrogradely back to the atrium by the accessory pathway This route of re entry requires that some portion of the ventricle be activated prior to retrograde conduction to the atria However in some cases the SVT may result entirely from re entry within the A V node which is suggested by the following (1) initiation of a SVT (with low to high atrial sequence of activation) following a premature atrial beat which antegradely blocks within the HPS, i e, no ventricular depolarization[1], A V nodal re entry is also suggested when a functional A V block within the HPS occurs during a sustained tachycardia (Fig 5 of Part II) (2) if during a SVT, retrograde activation of the atria (Ae) precedes ventricular depolarization (i e, H Ae < H V interval), it is unlikely that retrograde conduction via a Kent bundle is required to sustain the tachycardia (Fig 3 of Part II), (3) initiation of a SVT (with low to high sequence of atrial activation) during an A V nodal Wenckebach cycle in which criterion No 2 is satisfied i e atrial activation of echo beats precedes ventricular depolarization, (4) when incremental ventricular pacing reveals exclusive retrograde conduction via the normal A V conduction system[13]

Utilization of the accessory pathway for retrograde conduction to the atria during a SVT with normal QRS complexes is suggested by the following (1) A short constant V A interval over a full range of incrementally paced ventricular rates The suggestion that retrograde conduction is occurring via an accessory pathway is more firmly established when during premature ventricular stimulation it can be demonstrated that the V A interval remains constant and short, and retrograde atrial activation (A_2) precedes a delayed retrograde His bundle activation (H_2) (2) If during a SVT a single ventricular beat oc

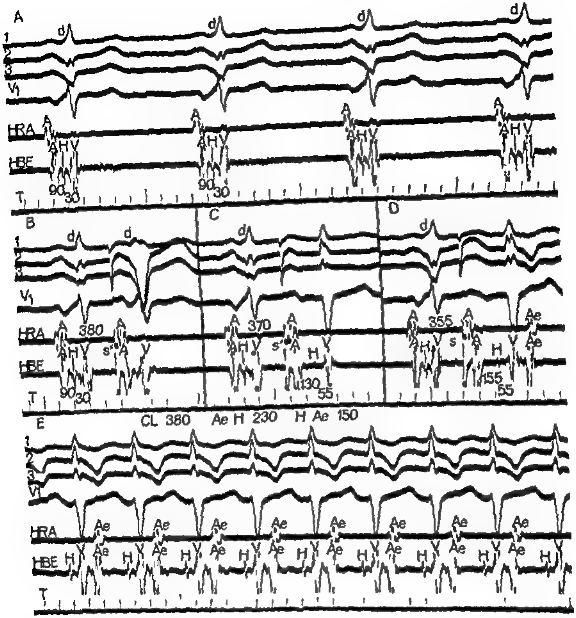

Fig 2 Effects of atrial premature stimulation in WPW syndrome Panel *A* shows sinus rhythm The A H and H V intervals measure 90 and 30 msec respectively The superior orientation of the delta wave mimics a diaphragmatic myocardial infarction (Q waves in Leads II and III) Panels *B* to *D* show the effects of progressive premature atrial beats on ventricular excitation The premature beat in panel *B* results in more pre excitation (the *H* deflection is obscured by ventricular electrogram) In panel *C* at an atrial coupling interval of 370 msec the accessory pathway is refractory and conduction occurs over the normal pathway resulting in a normalized QRS complex (slightly aberrant) In panel *D* an earlier premature beat conducts exclusively over the normal pathway and returns to the atria (Ae) via the accessory pathway which initiates a sustained SVT (panel *E*) The narrow QRS complexes and H V interval in panel *E* suggest that ventricular activation during the SVT occurred over the normal pathway Note also the absence of Q waves in Leads II and III during the tachycardia

curring simultaneously with or following shortly after the antegrade His bundle depolarization results in a shorter atrial cycle length with similar atrial activation sequence as during the spontaneous SVT (3) If the rate of SVT during the development of a functional bundle branch block is less than during normal ventricular activation [5, 6] This observation not only suggests retrograde conduction via an accessory pathway but also indicates whether the site of insertion of

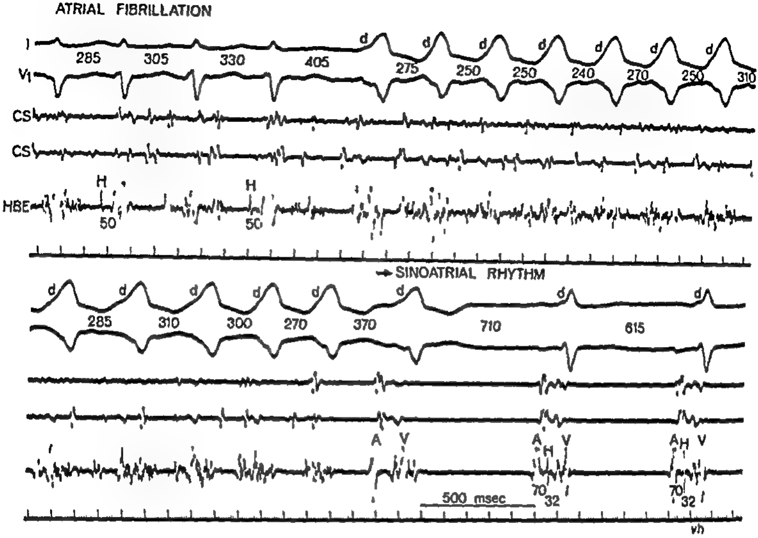

Fig 3 Atrial fibrillation in the WPW syndrome The top panel shows that during atrial fibrillation ventricular activation initially occurs exclusively over the normal pathway as indicated by the absence of delta narrow QRS complexes and H V intervals of 50 msec (first four beats) Subsequently ventricular activation occurred over the accessory pathway (wide QRS complexes) which mimics a ventricular tachycardia The bottom panel shows spontaneous termination of atrial fibrillation Note ventricular pre excitation during sinus beats

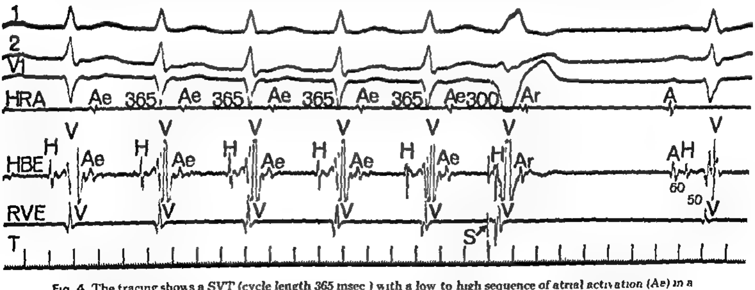

Fig 4 The tracing shows a SVT (cycle length 365 msec) with a low to high sequence of atrial activation (Ae) in a patient without evidence of WPW syndrome A premature ventricular beat (S) introduced during the SVT conducts to the atria (Ar) and results in a similar atrial activation sequence The atrial cycle length is shortened to 300 msec and the SVT is terminated The constant H H intervals prior to termination of the tachycardia suggest that the last H deflection results from antegrade depolarization and was unaffected by the premature ventricular beat Thus retrograde activation of the atria by the premature ventricular beat in all probability occurred via anomalous pathway which was not operative antegradely

the bypass tract is into the left or right ventricle This is especially true if a contralateral bundle branch block has no influence on the rate of SVT

If a patient with a left ventricular bypass connection develops LBBB during a re entrant SVT delayed left ventricular activation will result in delayed activation of the atria via the left sided bypass *If such a patient develops a* functional right bundle branch block the atrial rate during the SVT will be unaffected Re entrant circuits located entirely in the A V node are independent of conduction delay or block within the HPS Therefore atrial rates in A V nodal re-entrant SVT do not change with the onset of functional block in the HPS It must be emphasized that ventricular rates in A V nodal re entrant SVT may vary if functional block in the HPS is associated with variable H V prolongation or complete failure of conduction in the HPS (Fig 5, of Part II)

With the use of some of the above criteria it is possible to accumulate evidence that in some patients without evidence of antegrade ventricular pre-excitation on the standard ECG re entrant supraventricular tachycardias utilize a retrograde bypass tract (Fig 4)

It should be noted that anatomic localization of re-entrant circuits in patients with WPW syndrome is of more than academic interest since surgical treatment is being used increasingly in those patients with disabling re entrant tachycardias which are refractory to medical therapy [7]

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Drugs in the management of hypertension Part I

Lot B Page M D
Henry M Yager, M D
James J Sidd, M D
Newton and Boston Mass

The importance of detecting and treating asymptomatic hypertension has belatedly dawned on the medical profession and the public almost simultaneously It is still repugnant to both physicians and patients, that persons who feel well and are living active and productive lives should be given expensive and complex medication programs which frequently cause disagreeable side effects in order to reduce the risk of catastrophes which seem remote and theoretical Nevertheless, the compelling evidence that elevated blood pressure even of mild degree is associated with enhanced risk of cardiovascular disease [1] and that the risk is substantially reduced by lowering blood pressure[2,3] cannot be ignored Furthermore high blood pressure is the most potent single risk factor in which intervention is both feasible and effective

For the vast majority of hypertensive patients good blood pressure control can be achieved with combinations of the antihypertensive medications currently available Nevertheless, the imperfections of the antihypertensive drugs are evident All are capable of causing side effects within the ordinary dose range and most require multiple dose schedules A high degree of patient compliance is required to follow these programs and in some patients satisfactory control is difficult or impossible to achieve even with multiple drug therapy New potent drugs still undergoing clinical tests give promise for better and more trouble free control Even so the goal of uniformly effective, simple and symptom free drug therapy of hypertension still seems far away

An even more distant goal is to prevent the development of an age related rise in blood pressure which is the precursor of primary hypertension Evidence suggesting that a preventive approach is possible has previously been reviewed [4]

Physiological studies on large numbers of hypertensive patients in recent years indicate that a heterogeneous variety of abnormalities is involved in sustaining elevated blood pressure Under controlled conditions patients appear to vary in the extent to which abnormalities in peripheral resistance cardiac output, plasma volume the renin–angiotensin–aldosterone system and the sympathetic nervous system contribute to elevated blood pressure [5] Antihypertensive medications vary in their mode of action and can be chosen specifically to oppose these abnormalities This has raised hopes that appropriate drugs can be specifically fitted to individual patients [5,6] On the other hand physiologic profiles may vary over time in individual patients and side effects of drugs as well as degree of hypotensive responses still cannot be accurately predicted for all patients Eventually, predictive fitting of treatment programs may become possible At present, drug programs must be individualized based on patients' responses Individual programs nevertheless should be based on knowledge of the pharmacology of the antihypertensive drugs Tranquilizers and sedatives have no established role in the treatment of hypertension, and their use should be discouraged

Diuretics

A wide variety of diuretic drugs exhibit sustained antihypertensive action The mechanisms by which they lower blood pressure are not thoroughly understood The orally administered diuretics have their major actions at one of

From the Departments of Medicine Newton Wellesley Hospital and Tufts University School of Medicine Newton and Boston Mass

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Reprint requests to Lot B Page M D 2000 Washington St Newton Lower Falls Mass 02162

Table I Classification of diuretics

Major site of action		*Generic name*	*Trade name ( )*	*Effective oral dose range mg/day*	*Commercially available dose (mg)*
Group I	Loop of Henle	Ethacrynic acid	Edecrin	50-?*	25, 50
		Furosemide	Lasix	40-?*	20, 40
Group II	Cortical diluting segment	Chlorothiazide	Diuril	500-1000	250, 500
		Hydrochlorothiazide	Hydrodiuril, Esidrix, Oretic	50-100	25, 50
		Hydroflumethiazide	Saluron	25-50	50
		Bendroflumethiazide	Bunoron, Naturetin	2-5	2, 5, [illegible]
		Benzthiazide	Exna	25-50	50
		Trichlormethiazide	Metahydrin, Naqua	4-8	2, 4
		Methyclothiazide	Enduron	5-10	2.5, 5
		Polythiazide	Renese	4-8	1, 2, 4
		Cyclothiazide	Anhydron	1-6	2
		Chlorthalidone	Hygroton	50-100	50, 100
		Quinethazone	Hydromox	50-?00	50
		Metolazone	Zaroxolyn	1-5	2, 5, 5
Group III	Distal tubule and collecting duct	Spironolactone	Aldactone	100-400†	25
		Triamterene	Dyrenium	100-?00	100
		Amiloride			Not available in U.S.A.

* No upper dose limit established, see text.
† Usual dose = 100 mg/day. Larger doses used in primary hyperaldosteronism and low renin hypertension, see text.

the three sites along the renal tubule (see Table I): these are (1) the ascending limb of Henle's loop, (2) the cortical diluting segment, and (3) the distal tubule and collecting duct. Diuretic potency is greatest for the "loop diuretics" (group I), intermediate for benzothiadiazines and other compounds which act on the cortical diluting segment (group II), and weakest for the agents which act on the distal tubule and collecting duct (group III).

Group I. The "loop diuretics," *furosemide* and *ethacrynic acid*, inhibit salt and water reabsorption by the ascending limb of Henle's loop. Reabsorption of sodium and chloride in this segment of the tubule is accompanied by limited passive reabsorption of water. This process is an essential feature of the urinary concentration and diluting mechanisms. The loop diuretics therefore interfere with both the concentrating and diluting ability of the kidney. Until recently, chloride reabsorption was thought to be a passive consequence of active sodium reabsorption throughout the renal tubule. However, recent studies indicate that in the thick ascending limb of Henle's loop chloride is the actively reabsorbed ion. Burg has shown that the major action of both furosemide and ethacrynic acid is inhibition of active chloride transport in this segment.

Group II. The diuretic agents in this group exert their major diuretic action on the cortical diluting segment of the renal tubule distal to the loop of Henle. Included are chlorothiazide and its congeners and the non-thiazide compounds chlorthalidone, quinethazone and metolazone. Maximal dilution of the urine is prevented by these agents, but concentrating ability is unaffected. The agents in groups I and II all increase excretion of sodium chloride and potassium.

Group III. The distal diuretics spironolactone, *triamterene* and amiloride inhibit sodium reabsorption at aldosterone-sensitive sites in the distal tubule and collecting duct. Sodium reabsorption in this segment of the tubule is linked to secretion of potassium and hydrogen ion. Spironolactone competitively inhibits the action of aldosterone, whereas the actions of triamterene and amiloride are unrelated to the presence of aldosterone.

Antihypertensive effects of diuretics. Initially the diuretics produce negative sodium and water balance, resulting in a fall in body weight, extracellular fluid and plasma volumes, and cardiac output. Renal blood flow and glomerular filtra

Drugs in the management of hypertension Part I

Lot B Page, M D
Henry M Yager, M D
James J Sidd M D
Newton and Boston Mass

The importance of detecting and treating asymptomatic hypertension has belatedly dawned on the medical profession and the public almost simultaneously It is still repugnant to both physicians and patients, that persons who feel well, and are living active and productive lives should be given expensive and complex medication programs which frequently cause disagreeable side effects, in order to reduce the risk of catastrophes which seem remote and theoretical Nevertheless, the compelling evidence that elevated blood pressure, even of mild degree, is associated with enhanced risk of cardiovascular disease [1] and that the risk is substantially reduced by lowering blood pressure [2,3] cannot be ignored Furthermore, high blood pressure is the most potent single risk factor in which intervention is both feasible and effective

For the vast majority of hypertensive patients good blood pressure control can be achieved with combinations of the antihypertensive medications currently available Nevertheless the imperfections of the antihypertensive drugs are evident All are capable of causing side effects within the ordinary dose range and most require multiple dose schedules A high degree of patient compliance is required to follow these programs and in some patients satisfactory control is difficult or impossible to achieve even with multiple drug therapy New, potent drugs still undergoing clinical tests give promise for better and more trouble free control Even so the goal of uniformly effective, simple and symptom free drug therapy of hypertension still seems far away

An even more distant goal is to prevent the development of an age related rise in blood pressure which is the precursor of primary hypertension Evidence suggesting that a preventive approach is possible has previously been reviewed [4]

Physiological studies on large numbers of hypertensive patients in recent years indicate that a heterogeneous variety of abnormalities is involved in sustaining elevated blood pressure Under controlled conditions, patients appear to vary in the extent to which abnormalities in peripheral resistance cardiac output plasma volume the renin-angiotensin-aldosterone system and the sympathetic nervous system contribute to elevated blood pressure [5] Antihypertensive medications vary in their mode of action, and can be chosen specifically to oppose these abnormalities This has raised hopes that appropriate drugs can be specifically fitted to individual patients [5,6] On the other hand physiologic profiles may vary over time in individual patients and side effects of drugs as well as degree of hypotensive responses still cannot be accurately predicted for all patients Eventually, predictive fitting of treatment programs may become possible At present, drug programs must be individualized based on patients responses Individual programs nevertheless should be based on knowledge of the pharmacology of the antihypertensive drugs Tranquilizers and sedatives have no established role in the treatment of hypertension and their use should be discouraged

Diuretics

A wide variety of diuretic drugs exhibit sustained antihypertensive action The mechanisms by which they lower blood pressure are not thoroughly understood The orally administered diuretics have their major actions at one of

From the Departments of Medicine Newton Wellesley Hospital and Tufts University School of Medicine Newton and Boston Mass

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Reprint requests to Lot B Page M D 2000 Washington St Newton Lower Falls Mass 02162

acid promotes rapid excretion of sodium and is particularly useful in the treatment of acute pulmonary edema associated with hypertension

2 In hypertensive emergencies intravenous loop diuretics are useful adjuncts to therapy with intravenous vasodilators to counteract the strong sodium retaining effect of these agents

3 When large doses of such drugs as alpha methyl dopa hydralazine or minoxidil are used the resultant renal tubular sodium reabsorption may vitiate the antihypertensive action of these drugs when even maximal doses of less potent diuretics are used concomitantly Substitutions of loop diuretics for the group II and III diuretics in such patients may result in weight loss and improved blood pressure control

4 In hypertensive patients with renal insufficiency the high potency of the loop diuretics may be required to achieve adequate volume contraction In such patients an initial rise in blood urea nitrogen and creatinine is often followed by stabilization in renal function

Distal diuretics Some investigators have found spironolactone in doses of 100 mg daily to be as effective as thiazides or chlorthalidone in the treatment of unselected primary hypertension Others have reported less marked reduction of blood pressure with spironolactone[3] Conflicting data have also been published concerning whether spironolactone and thiazides have additive antihypertensive properties[33] The antipressor effect of triamterene has been reported to be weaker than hydrochlorothiazide and chlorthalidone[3]

Occasionally in patients treated with a group I or group II diuretic secondary sodium retention and rise in blood pressure toward pre treatment levels may occur This may result from a brisk rise in aldosterone secretion induced by volume contraction In this situation the addition of spironolactone or triamterene may cause a modest diuresis and improved blood pressure control Distal diuretics also counteract the kaliuretic effects of the other oral diuretics However the commercially available combinations of a thiazide and spironolactone or triamterene do not reliably maintain the serum potassium within the normal range and serum potassium should be determined frequently when any diuretic regimen is initiated

Recently the use of spironolactone in the diagnosis and management of hypertension associated with primary hyperaldosteronism and low plasma renin activity has been advocated[7,3,40] Spark and Melby[3] reported that high doses of spironolactone produced marked weight loss and normalization of blood pressure in patients with primary hyperaldosteronism but not in those with secondary hyperaldosteronism while correcting the electrolyte abnormalities in both groups They concluded that spironolactone acts in patients with primary hyperaldosteronism by a direct inhibitory effect on aldosterone activity Bravo and colleagues hold an opposing view that spironolactone works non specifically to produce plasma and extracellular fluid volume depletion in these patients They have demonstrated blood pressure responsiveness to volume depletion and salt restriction in patients with primary hyperaldosteronism as well as an additive effect of thiazide and spironolactone on blood pressure in this group [1] Spironolactone has been found highly effective in lowering blood pressure in patients with primary hypertension and low plasma renin levels (low renin hypertension) but relatively ineffective in patients with normal renin levels Several other crossover studies have shown the low plasma renin activity group to respond as well to hydrochlorothiazide or chlorthalidone as to spironolactone [4] In these studies the blood pressure response to either drug was better in the low plasma renin activity group A smaller percentage of patients with normal plasma renin activity also responded to both agents

Adverse effects All of the agents in groups I and II may induce hypokalemia and metabolic alkalosis In some patients a high dietary potassium intake is adequate to maintain normal potassium balance However many will require supplemental potassium chloride in doses of 40 to 80 mEq per day or addition of a potassium sparing group III diuretic to the regimen The more potent diuretics may produce volume depletion and hyponatremia

Hyperuricemia is a common side effect of any of the agents in groups I and II The use of thiazides raises the already high incidence of hyperuricemia among primary hypertensive patients from 25 to 35 per cent to 65 to 70 per cent[44] Unless associated with a pre existing history of gout or the development of gouty attacks after initiating therapy asymptomatic hyperuricemia probably need not be treated

tion rate also fall slightly[11] and plasma renin activity increases. These effects occur in normotensive as well as in hypertensive subjects. In hypertensive patients these changes are accompanied by a fall in blood pressure, whereas no significant blood pressure reduction occurs in normotensive subjects. Dietary salt restriction has similar antihypertensive actions.

Over a three to four week period of diuretic treatment, cardiac output slowly returns to normal and plasma and extracellular fluid volume increase. It is likely that enhanced proximal tubular reabsorption in response to the initial volume depletion plays an important role in this readjustment. Stimulation of the renin-angiotensin-aldosterone system may also play a role.

Studies of total exchangeable sodium balance, ECF and water balance in patients on long term thiazide therapy have shown a return to pretreatment values.[1, 11] Recent studies[1, 18] have demonstrated a persistent small reduction of extracellular fluid and plasma volumes. Small reductions of glomerular filtration rate (GFR) also persist.

A major factor in sustaining the antihypertensive effect of diuretics appears to be the slow development of diminished peripheral resistance. Several mechanisms to account for this change have been postulated. These include salt and water depletion of the arteriolar wall, an effect on autonomic control of vascular tone, and an effect on vascular smooth muscle reactivity. These theories remain to be substantiated. Thiazides have been shown to reduce vascular reactivity to norepinephrine and angiotensin. Conflicting data have been published on the effect of these diuretics on electrolyte content of arterial tissues.

Although diuretics may reduce blood pressure through several mechanisms, strong evidence presently exists only for the role of persistent reduction of total body sodium content and plasma volume.

Uses. Oral diuretics should be the cornerstone of most antihypertensive regimens. Mild to moderate hypertension is often controllable with a diuretic alone. In more severe hypertension these agents have been shown to enhance the effects of the other antihypertensive drugs, most of which can cause salt and water retention.

Diuretics are generally well tolerated. The polyuria which they induce lasts only days to a few weeks in non edematous patients. In contrast to many antihypertensive agents, diuretics produce no significant postural hypotension, and they are not associated with the development of tachyphylaxis.

When used alone, diuretics lowered blood pressure significantly in 40 to 66 per cent of patients in different series.[17, 18] Conway and Lauwers[17] reported an average reduction of 26/17 mm Hg. Patients with diastolic pressures below 110 mm Hg were frequently rendered normotensive. Severe hypertension is not likely to be controlled with diuretics alone. However, several reports indicate that the same dose of diuretic results in a greater fall in blood pressure in severe than in mild hypertension.[18, 19]

Choice of diuretic agent and dosage. To achieve smooth reduction of blood pressure all of the oral diuretics must be administered at least once daily. Maximum effectiveness is achieved only after three to four weeks of therapy.

The thiazides were introduced in 1957 and have been the most widely used diuretics in the treatment of hypertension. Among the available pharmacologic preparations in group II, chlorothiazide 0.5 to 1.0 Gm. daily, hydrochlorothiazide 50 to 100 mg. daily, and chlorthalidone 100 to 200 mg. daily have been shown to have comparable potency. The other members of group II appear to have equivalent antihypertensive activity. Metolazone 2.5 mg. daily has antihypertensive effects comparable to hydrochlorothiazide, but experience with the drug is limited. Although thiazides can measurably reduce GFR when given parenterally,[11] this effect is negligible following oral administration.

Loop diuretics. Most comparative studies indicate that the antihypertensive potency of group I and group II diuretics are equivalent.[21, 3] One recent crossover trial found hydrochlorothiazide more effective than furosemide in hypertension. The greater diuretic potency of loop diuretic increases the risk of severe volume contraction, hypokalemia, and metabolic alkalosis when compared to the less potent group II drugs. In edematous, azotemic, or refractory hypertensive patients no ceiling dose has been established for loop diuretics. Their use should probably be reserved for the following clinical situations:

1. Hypertensive patients with congestive heart failure whose extracellular fluid volume cannot be adequately controlled with less potent diuretics. Intravenous use of furosemide or ethacrynic

hydrochlorothiazide and furosemide in the treatment of hypertensive patients Q J Med. 40 541 19 1

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Carbohydrate intolerance develops in some patients This is generally not a clinical problem except in diabetic patients who may require adjustment of hypoglycemic therapy

There is a low incidence with these agents of serious allergic reactions such as thrombocytopenia leukopenia or vasculitis Rarely thiazides have caused cholestatic jaundice and toxic pancreatitis

Ethacrynic acid and furosemide can produce reversible hearing loss when used in high doses Several cases of permanent hearing deficit have been reported after ethacrynic acid administration Suggestive evidence also links furosemide to irreversible deafness [4]

Spironolactone and triamterene may induce serious hyperkalemia when not given concurrently with another diuretic or when given to patients taking high dietary potassium intake or potassium supplements including salt substitutes The risk of hyperkalemia is particularly great when these agents are used in the presence of renal insufficiency, and severe renal failure contraindicates their use

Triamterene may produce gastrointestinal upset This is generally overcome by taking doses at mealtimes A rare complication of triamterene is an anemia of folic acid deficiency

Spironolactone can cause dose related decreased libido gynecomastia and impotence in the male menstrual irregularities and breast enlargement in the female Lassitude may also be seen with high doses of spironolactone

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Historical Note

N C Korotkoff—1874-1920—Pioneer vascular surgeon

Harold N Segall M D
Montreal Quebec Canada

Dr N C Korotkoff the surgeon who discovered the brachial artery sounds by which arterial pressure is measured has other accomplishments to his credit Indeed, the auscultatory technique developed out of his experimental work on collateral circulation[1] Recently, evidence has come into view which establishes Korotkoff as a significant pioneer of twentieth century vascular surgery

An ordinary clinical experience triggered my interest in Korotkoff's work and biography One day in May, 1939 during a house call after applying the Riva Rocci cuff I had to improvise in order to measure both diastolic and systolic pressure levels because I had no stethoscope having left it in my office The idea of palpating the sounds over the brachial artery proved effective[2] A few days later searching the literature for Korotkoff's original description of the method it became apparent that although the reference appeared in many bibliographies the article itself could not be found No author mentioned anything about the manner in which Korotkoff discovered the brachial artery sounds and no reference to palpation of the sounds could be found In 1941 William Hall Lewis Jr[3] shed light on the subject by publishing a translation of the original article Korotkoff had reported his method at a regular staff meeting of the Military Medical Academy of St Petersburg His brief description (281 words) and the longer discussions by several colleagues were published in the transactions of these meetings Lewis found the appropriate volume in the Slavonic division of the New York Public Library This document did not contain any reference to how it came about that Korotkoff thought of listening over the brachial artery to measure arterial pressure

During the only visit I have made to Russia (in 1962) I enquired from physicians and librarians in Leningrad, Moscow and Kiev and found no clue to biographical information about Korotkoff nor to how he discovered his method of measuring arterial pressure However, a lady on the staff of the great state library in Leningrad undertook to send me information if she could find any Two years later she did send me a typewritten copy of a biographical sketch which I subsequently learned had been delivered at a special meeting in 1955 in commeration of the 50th anniversary of Korotkoff's discovery I published the contents of this sketch with some comments about Korotkoff's importance in the history of modern medicine to the effect that he merits more prominence in the limelight than he appears to have had during his lifetime[4] Two years after the publication of this article I received a letter from Professor M Multanowsky professor of Medical History at the Pirogoff Medical Institute in Moscow He referred to the above comments and wished to inform me that in Russia Korotkoff's importance is appreciated He drew my attention to the special meeting of the Leningrad Branch of the S O Botkin Therapeutical Association at which Dr V P Nikitin delivered the memorial address which contained the biographical sketch This initiated correspondence with Professor Multanowsky in which I was able to tell him of my search for information about how Korotkoff had made his discovery I had borrowed a copy of Korotkoff's thesis for the doctorate had it translated into English and hoped to publish this I enquired as to whether it would be possible for me to have a photograph of Korotkoff for a frontispiece to this publication Two years later (December 1969) he sent me a treasure trove At his suggestion two medical historians in Leningrad Drs Sonvoronova and Kogan undertook to search for a relative of Korotkoff who might have a photograph They found his son Dr S N

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Reprint requests Harold N Segall M D 5845 Cote des Neiges Rd Suite 235 Montreal Quebec H3S 1Z4 Canada

Korotkoff who gave them the only photograph he could find at that time It was a postcard sized picture of the Russian Red Cross Unit in which his mother and father served during the Russo Japanese War The photograph was taken before the departure from St Petersburg (Leningrad) to Harbin Manchuria Dr Multanowsky sent me a copy of this picture as well as an enlargement of the little figure of Korotkoff and also the son s address

In correspondence with the son I learned that he is a specialist in rehabilitation and sport medicine and he sent additional precious pictures one photograph of his mother alone in ordinary dress of the period (1904) a copy of the group mentioned above with identification of his mother and father and pictures of the hospital in Harbin where his father worked as a surgeon and his mother as a nurse

In 1975 a colleague doing research in Leningrad interviewed Dr S N Korotkoff on my behalf to gather additional biographical data on his father * Thus after an interval of about six years our correspondence was resumed with a letter I received from Dr Korotkoff in December 1975 in which he reported that a meeting was held by the Leningrad Society of Therapeutics in 1974 to honour the 100th anniversary of his father s birth and in which he told of the discovery of a photograph of his father taken during his student days He very graciously sent me a copy of this picture He mentions an important fact namely that his father was interested in vascular surgery before his departure for Manchuria During his service at the front cases of vascular wounds were referred to him Forty one of the 44 case reports published in his thesis for the doctorate were part of his war experience in the hospital at Harbin

Five years elapsed between 1905 when Korotkoff was performing the experimental work on determining the efficiency of arterial collaterals and 1910 the year in which he successfully defended his thesis for the doctorate In the first chapter of this thesis which is entitled Introduction we find the following In one of his latest works Matas who strongly favours reconstructive surgery studied the problem of determining the efficiency of arterial collaterals and as a result

Fig 1

suggested that only in rare cases those definitely threatened with gangrene because of inadequate collateral circulation should resection of the wounded vessel and suturing of the ends to preserve the lumen be tried

Matas introduced the concept re effectiveness of collaterals—and measuring this concerns Korotkoff in his work for this thesis

During those 5 years Korotkoff reflected on the facts that he had gathered in the course of his surgical experience and from the results of the experimental work he had done and this led him to write the following in the concluding paragraph of the introduction I wish to state that I am mainly in favour of any attempt to preserve a blood vessel lumen and I believe that at some time in the future an adequate functioning of the blood vessels will be secured in a higher

*I am indebted to Dr N Frieden Marymount Manhattan College for arranging the interview and sending me a transcript of his conversation with S N Korotkoff

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Montreal Quebec Canada

Dr N C Korotkoff, the surgeon who discovered the brachial artery sounds by which arterial pressure is measured, has other accomplishments to his credit. Indeed the auscultatory technique developed out of his experimental work on collateral circulation.[1] Recently evidence has come into view which establishes Korotkoff as a significant pioneer of twentieth century vascular surgery.

An ordinary clinical experience triggered my interest in Korotkoff's work and biography. One day in May 1939 during a house call, after applying the Riva Rocci cuff, I had to improvise in order to measure both diastolic and systolic pressure levels because I had no stethoscope having left it in my office. The idea of palpating the sounds over the brachial artery proved effective.[2] A few days later, searching the literature for Korotkoff's original description of the method it became apparent that although the reference appeared in many bibliographies the article itself could not be found. No author mentioned anything about the manner in which Korotkoff *discovered the brachial artery sounds and no* reference to palpation of the sounds could be found. In 1941 William Hall Lewis Jr[3] shed light on the subject by publishing a translation of the original article. Korotkoff had reported his method at a regular staff meeting of the Military Medical Academy of St Petersburg. His brief description (281 words) and the longer discussions by several colleagues were published in the transactions of these meetings. Lewis found the appropriate volume in the Slavonic division of the New York Public Library. This document did not contain any reference to how it came about that Korotkoff thought of *listening over the brachial* artery to measure arterial pressure.

During the only visit I have made to Russia (in *1962) I enquired from physicians and librarians in* Leningrad, Moscow *and Kiev and found no clue* to biographical information about Korotkoff nor *to how he discovered his method of measuring* arterial pressure. However, a lady on the staff of the great state library in Leningrad undertook to send me information *if she could find any*. Two years later, she did send me a typewritten copy of a biographical sketch which I subsequently learned had been delivered at a special meeting in 1955 in commeration of the 50th anniversary of Korotkoff's discovery. I published the contents of this sketch with some comments about Korotkoff's importance in the history of modern medicine to the effect that he merits more prominence in the limelight than he appears to have had during his lifetime.[4] Two years after the publication of this article I received a letter from Professor M Multanowsky professor of Medical History at the *Pirogoff* Medical Institute in Moscow. He referred to the above comments and wished to inform me that in Russia Korotkoff's *importance is appreciated*. He drew my attention to the special meeting of the Leningrad Branch of the S O Botkin Therapeutical Association at which Dr V P Nikitin delivered the memorial address which contained the biographical sketch. This initiated correspondence with Professor Multanowsky in which I was able to tell him of my search for information about how Korotkoff had made his discovery. I had borrowed a copy of Korotkoff's thesis for the doctorate had it translated into English *and hoped to publish this*. I enquired as to whether it would be possible for me to have a photograph of Korotkoff for a frontispiece *to this publication*. Two years later, (December, 1969) he sent me a treasure trove. At his suggestion two medical historians in Leningrad Drs Sonvoronova and Kogan undertook to search for a relative of Korotkoff who might have a photograph. They found his son Dr S N

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Reprint requests Harold N Segall M D 5845 Cote des Neiges Rd Suite 235 Montreal Quebec H3S 1Z4 Canada

Korotkoff who gave them the only photograph he could find at that time It was a postcard sized picture of the Russian Red Cross Unit in which his mother and father served during the Russo Japanese War The photograph was taken before the departure from St Petersburg (Leningrad) to Harbin Manchuria Dr Multanowsky sent me a copy of this picture as well as an enlargement of the little figure of Korotkoff and also the son s address

In correspondence with the son I learned that he is a specialist in rehabilitation and sport medicine and he sent additional precious pictures one photograph of his mother alone in ordinary dress of the period (1904) a copy of the group mentioned above with identification of his mother and father and pictures of the hospital in Harbin where his father worked as a surgeon and his mother as a nurse

In 1975 a colleague doing research in Leningrad interviewed Dr S N Korotkoff on my behalf to gather additional biographical data on his father * Thus after an interval of about six years our correspondence was resumed with a letter I received from Dr Korotkoff in December 1975 in which he reported that a meeting was held by the Leningrad Society of Therapeutics in 1974 to honour the 100th anniversary of his father s birth and in which he told of the discovery of a photograph of his father taken during his student days He very graciously sent me a copy of this picture He mentions an important fact namely that his father was interested in vascular surgery before his departure for Manchuria During his service at the front cases of vascular wounds were referred to him Forty one of the 44 case reports published in his thesis for the doctorate were part of his war experience in the hospital at Harbin

Five years elapsed between 1905 when Korotkoff was performing the experimental work on determining the efficiency of arterial collaterals and 1910 the year in which he successfully defended his thesis for the doctorate In the first chapter of this thesis which is entitled Introduction we find the following In one of his latest works Matas who strongly favours reconstructive surgery studied the problem of determining the efficiency of arterial collaterals and as a result

Fig 1

suggested that only in rare cases those definitely threatened with gangrene because of inadequate collateral circulation should resection of the wounded vessel and suturing of the ends to preserve the lumen be tried

Matas introduced the concept re effectiveness of collaterals—and measuring this concerns Korotkoff in his work for this thesis

During those 5 years Korotkoff reflected on the facts that he had gathered in the course of his surgical experience and from the results of the experimental work he had done and this led him to write the following in the concluding paragraph of the introduction I wish to state that I am mainly in favour of any attempt to preserve a blood vessel lumen and I believe that at some time in the future an adequate functioning of the blood vessels will be secured in a higher

* I m ind bted to D N Fned n M rym t Manhattan Coll g f r arr ging h terview d send g me t anscript f h on ersa tion with S N Korotk ff

percentage of cases involving the problem of resection '

In 1915, Osler spoke of Rudolph Matas the Father of Modern Vascular Surgery He declared the results of the last wars should be carefully studied by our surgeons and may I refer the younger army surgeons to the section on aneurysms in Keen's Surgery, by that modern Antyllus my old and valued friend Rudolph Matas of New Orleans Now we can count N C Korotkoff as an early Matas colleague

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Instrumentation performance testing
A prerequisite for hospital safety

Electrical hazards in a hospital environment resulting from microshock or macroshock have gained notoriety in the last few years as a result of coverage in scientific literature the news media and lay press, and the involvement of consumer groups. It has been estimated that between 1,200 and 5 000 electrocutions occur annually as a result of electrical hazards in a hospital environment As a result of this gloomy picture strong recommendations have been made for the development of safety programs, the training of personnel and the periodic evaluation of all equipment[1-]

It is presumed that a safety program assuring the absence of electrical shock hazards will result in a safe environment in which case the use of medical instrumentation will no longer be associated with any potential mishaps of serious consequence It is important to question the adequacy of these efforts and the narrowness of the current definition of electrical safety Confining our concern to the prevention of electrocution we are ignoring an area of critical importance namely the effect of instrumentation performance as a cause of diagnostic or therapeutic error The improper calibration, misalignment or the malfunction of equipment resulting in erroneous determinations or the sudden equipment failure in emergency situations when no provisions for backup systems exist also constitute a safety hazard These problems also constitute a potential liability for the patient the physician the hospital and ancillary personnel, in that their prevalence has not been accurately established nor their significance stressed to the medical profession. Such problems have in the recent past, resulted in large awards by the courts or in out of court settlements, as an indication of irreparable damage induced by the unjustified malfunction or inaccuracy of an electronic device[1-]

The preceding discussion indicates that these malfunctions do not constitute isolated instances, and emphasizes the need to establish provisions to insure that instrumentation utilized in clinical environments performs with predetermined reliability and its performance is inspected at regular intervals

The existing problem is, therefore clearly defined hospital safety cannot be equated with electrical safety and therefore the approach utilized in most institutions fails to satisfy minimum requirements. Hospital safety requires periodic maintenance and calibration of electrical equipment in addition to the regular electrical safety inspections for current leaks, grounding problems and shock hazards.

How is it that the medical profession and its paramedical associates have allowed this situation to occur? The answer is not simple since all the three prime participants are involved, namely (1) the user who unaware of the potential malfunctions, expects hardware to perform always to manufacturers specifications (2) the hospital and its management who have not accepted direct responsibility in this area and failed to keep pace with the growth of medical technology and (3) the manufacturer who has rarely provided simple and applicable testing features for maintenance checks, and has not designed tests and instructions enabling the user to periodically measure equipment performance

The imperative solution to the problems outlined are twofold (1) To bring into hospitals the clinical engineers who can lift "safety" out of the power leakage level into the performance level, and (2) To have the equipment better designed for performance level testing with adequate procedures, access points, and reference material provided.

To obtain adequate people will require a long process of continuing education for medical administration and paramedical personnel. Hospitals may have to establish clinical engineering laboratories according to their sizes and medical needs. Small community hospitals will benefit from combining their resources and perhaps establishing a full time service organization to serve this purpose in a regional manner Progress in these areas is already being noted and such services are available from several non profit organizations operating on a community basis.

On the other hand, from the manufacturer aspect the specified test procedures normally require the use of comparatively complex test equipment they also involve the considerable expenditure of time Neither of these conditions can be tolerated in patient care areas, and either a remote test laboratory must be set up or the instrumentation will just not be tested. The latter condition often subsists. In some instances the manufacturer's recommended test procedures may demand approximately two hours of testing time per bed or two weeks for a 28 bed unit a completely unacceptable situation in a busy clinical area Thus the equipment must be designed with adequate access points to allow simulated input signals to be introduced and outputs to be measured easily Frequent and major disassembly of equipment and its connectors can in itself lead to failures. Externally accessible test points are absolutely necessary for fast performance testing if we are to avoid disrupting the normal operational configuration at the bedside

Finally the reference material supplied by the manufacturers should consider the growing improvements of clinical engineering in the hospital setting and therefore provide schematic diagrams needed for developing first level test procedures which do not require a major expenditure of time and effort. These programs can be instituted with ease as shown by our experience at The George Washington University Medical Center where in place evaluation of the performance of the four cardiovascular monitoring instruments at each of the 3? beds in the Intensive Care Unit and Coronary Care Unit and the ancillary equipment in the ECG Laboratory is currently carried out on a regular basis. With a time constraint of not more than five minutes per bedside the procedures are designed simply to apply simulated pulses at the input to each instrument. The respective output levels are measured with the sensitivity controls of the instruments at

two known positions such as at their maximum and minimum positions These output levels are compared against the corresponding levels measured during prior months any variation indicating the need for a more in depth checkup

The cost for implementation of this program was $1 000 in hardware plus $5 00 per monthly check per bed Partially offsetting this cost is the significant reduction in equipment repair costs which result from repeated preventive maintenance Considering the potential liability risks the growing concern by insurance carriers and the improvement in patient care such programs appear highly cost effective and their implementation should be encouraged

Michael J Shaffer MSEE
Dept of Anesthesiology
Jorge C Rios MD
Dept of Medicine and
Director ECG Laboratory
C Herman Klingenmaier MD
Dept of Anesthesiology
George Washington University Medical Center
Washington D C

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The dynamic nature of the ST-T segment in ischemic heart disease

According to the prevailing concept dynamic changes in either normal or abnormal ST T segments in the resting ECG are not expected to take place unless transient myocardial ischemia occurs, and patients who exhibit alteration of a previously normal ST T segment or aggravation of a previously pathological segment are considered to have active ischemic heart disease or even to be at high risk of developing infarction[1] [2] Such ischemia is usually expected to be accompanied by chest pain To provoke alteration of the ST T segment various exercise tests are advocated

We challenge this static concept of the ST T segment since in our experience patients with ischemic heart disease show extremely wide variations in this segment during normal everyday activities at rest or even during sleep and very often without any accompanying chest pains[3,4] As demonstrated below patients with a normal resting ECG may have severe transient ST T abnormalities and patients with ST T alterations in the resting ECG may exhibit either aggravation or improvement in these changes during a 24 hour period

We examined 400 patients suspected or known to suffer from ischemic heart disease using the Holter monitoring technique during a 24 hour period of normal everyday activities Some of them had a normal and others an abnormal ST T segment in the resting ECG In most of those with a pathological resting ST T segment dynamic variations either improvement or aggravation were seen Chest pain was not frequently observed as an accompanying symptom in those showing aggravation

Illustrative ECG tracings of a 52 year old male patient are shown in Fig 1 This patient had atypical chest pain and during the 24 hour monitoring period exhibited various degrees of ST segment depression not accompanied by chest pain Fig 2 shows segments of the 24 hour ECG tracing of a 62 year old man who had a pathological resting ECG During the monitoring period aggravation of the ST segment depression and T wave inversion were observed Pain was experienced only during the early morning period and the concomitant tracing is shown in the bottom row The third example (Fig 3) is of a 56-year old man in whom minimal resting ST T changes became aggravated during various daily activities such as food intake (second row) or walking (fourth row) During night sleep (bottom row) the ECG returned to normal

We believe that the appearance of dynamic ST T changes during everyday activities is an expression of ischemic heart disease This assumption was confirmed by demonstrating good correlation between the dynamic ST T alterations revealed by the ambulatory ECG monitoring and the results of a multistage bicycle test[5] Moreover some of these patients underwent coronary arteriography and all those who exhibited dynamic ST T changes were found to have significant coronary artery disease[6]

The frequent dynamic alterations in the ST T segment during everyday activities and stresses even without precordial symptoms indicate that in these patients the balance between the oxygen supply and demand of the myocardium is so labile that periods of improvement and worsening appear even without exposing the patient to unusual exertion Moreover there are evidently stimuli other than exercise which can provoke ST T changes which are sometimes even

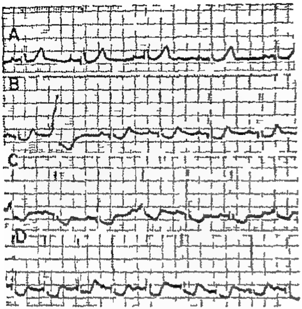

Fig 1 Normal ECG tracing during most of the Day (A) Various degrees of ST depression unaccompanied by chest pain (B C and D) Mental stress at work preceded the ST depression observed in D

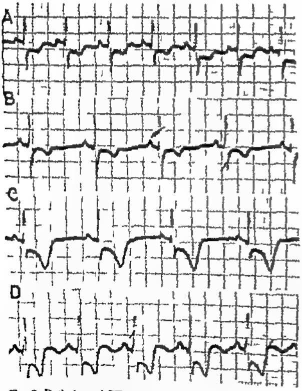

Fig 2 Pathological ST segment during most of the day (A) Slight improvement at rest (B) Marked aggravation during night sleep (C) and early morning (D) Only during the early morning period was chest pain experienced

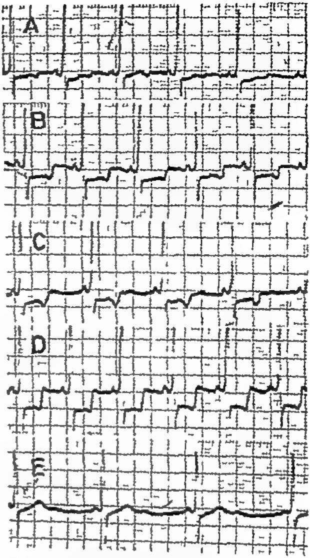

Fig 3 Slight ST T changes during most of the day (A) Various degrees of aggravation of the ST T pattern were observed after meals (B) at rest (C) and during walking (D) Pain was experienced only during the walking period During night sleep (E) ECG returned to normal

more drastic than those appearing during physical effort Without the use of continuous ambulatory ECG monitoring as a tool for evaluation and detection of ischemic heart disease these transient ischemic changes would remain unnoticed. The presence of a dynamic ST T pattern seems to be a common finding in coronary artery disease and is not necessarily a sign of sudden deterioration or acute aggravation of the disease. The concept of the ST T segment being static should, in our opinion, be abandoned and replaced by the more physiological concept of its dynamic nature

Shlomo Stern M.D
Dan Tzivoni M.D
Hadassah Hebrew University Medical Center
Jerusalem Israel

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Of a standard hospital chart

Why aren't the hospital charts throughout the U S A uniform in organization page coloring size and order of placement of the various components? The convenience and time saved alone for all who use them and work at different hospitals would justify having a uniform chart for all hospitals private and government The importance of exchange of clinical information in the care of patients assisted by rapid transportation greatly supports the need value and usefulness of uniform standard hospital charts throughout the country

G E Burch M D
Tulane University School of Medicine and Charity Hospital
New Orleans La

Practical advantages of two-channel electrocardiographic Holter recordings

In over 300 24 hour Holter recordings practical clinical advantages of utilizing a two channel Holter electrocardiographic recording system for ambulatory patients engaged in normal daily activities at home and at work were

1 *97 per cent reliability of recording electrocardiographic data* Technical failure to record electrocardiographic data may result from diminution of signal artifact and rarely complete loss of signal due to monitor lead breakage vigorous body movement body posture or (as occurs most commonly) inadequate lead fixation In our experience intermittent or complete failure to obtain interpretable electrocardiographic data occurred from channel one in 43 2 per cent (118 of 273) of recordings for 11 9 per cent (720 of 6054) of total hours monitored from channel two in 33 7 per cent (92 of 273) of recordings for 16 7 per cent (1 011 of 6 054) of total hours monitored and from both channels simultaneously in only 15 7 per cent (43 of 273) of recordings for 3 4 per cent (206 of 6 054) of total hours monitored Technician error induced malfunction of the recorder in 1 per cent (31 of 304) of total recordings which were excluded from consideration The practical advantages of two channel electrocardiographic recordings in conserving patient technician physician and equipment operation time by avoiding the need for repeat study are evident In addition the increased reliability of recording electrocardiographic data for a particular chance event is of great value

2 *Improved identification and recognition of anomalous cardiac beats* Utilizing two channels of electrocardiographic data (modified chest lead V or MCl and chest bipolar lead V or CB) has improved analysis of anomalous electrocardiographic complexes by (a) exposing a normal (Fig 1*A*) or slightly aberrant (Fig 1*B*) appearing electrocardiographic complex in one lead as anomalous in the other lead (b) allowing appreciation of concordancy of *QRS* axis in the V leads (Fig 1C) for identifying anomalous beats of ventricular origin and (c) distinguishing artifact induced anomalous complexes from true ectopic beats (Fig 1*D*)

3 *Improved detection of myocardial ischemia* Utilization of two electrocardiographic leads (a V like lead and an aV_r like lead) has allowed appreciation of ischemic ST segment

Avionics 24 hour Model 425 Electrocardiocorder and Model 660 Electrocardioscanner

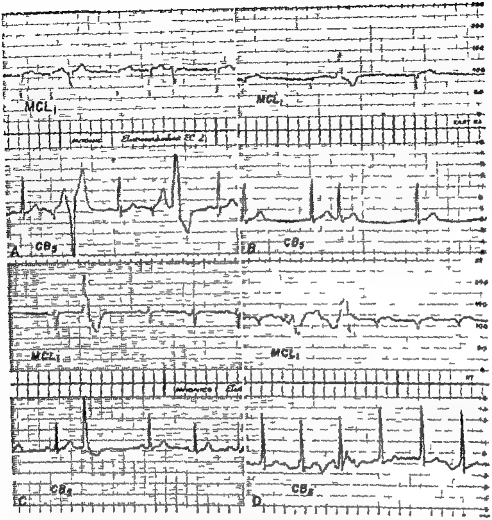

Fig 1 Simultaneously recorded electrocardiographic leads MCL and CB *A* the second and fifth QRS complexes recorded in lead MCL seem similar to the preceding sinus beats but lead CB discloses an apparent anomalous complex *B* the third QRS complex in lead CB appears to be premature and slightly aberrant but lead MCL indicates a more anomalous appearing complex *C* the anomalous QRS complex demonstrates concordancy of mean QRS axis *D* artifact induced anomalous complexes in lead MCL are more clearly defined by maintenance of detectable regular rhythm in lead CB

depression and elevation in both an antero lateral and an inferior myocardial plane thereby enhancing the detection of myocardial ischemia during Holter recording.

Harold L Kennedy M D
Stephen J Underhill
J Richard Warbasse M D
Cardiovascular Services and Laboratories
U S Public Health Service Hospital
Baltimore Md

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d viation We presented some data on this topic at the XIIth International Symposium of Vectorcardiography Although the selection criteria were slightly different the results of both studies compare favorably in many respects In our study 100 patients were selected out of a group of about 2 000 providing one of the following criteria were positive a frontal maximal vector oriented to 0 degrees or more superiorly and/or a QRS mean axis (A QPS) of −30 degrees or more superiorly There was a large range in the age of the patients with predominance for elderly patients 5(were older than 50 years, 27 older than 0 years. Our clinical diagnosis showed even more coronary atherosclerosis (66 per c nt) than in this paper 55 patients presenting with electrical signs of infarction In another 13 patients hypertension or cerebrovascular diseases were found Our number of patients with chronic pulmonary disease was much smaller but this might be due to a rather restricted number of such patients in our clinic our subsequent experience certainly agrees more with the data of the above mentioned paper

Left axis deviation due to loss of inferior forces is an interesting entity that is sometimes confused with left anterior hemiblock and is seldom mentioned in textbooks differential diagnosis with hemiblock could be made by clockwise rotation of the VCG loop in the frontal projection in all our cases moreover the loops of inferior infarction were located significantly lower than those of hemiblock and of hemiblock plus infarction (A QRS −3. degrees versus −55 degrees)

Th frequency of left ventricular hypertrophy and complete left bundle bran h block in our study as w ll as th study by Drs Grayzel and Neyshaboori was surprisingly low (3 patients of each) This illustrates that in contrast to what is mentioned in the older literature both these entities are not a frequent cause of left axis deviation

Denis L Clement M D
Academic Hospital
Department of Cardiology
De Pintelaan 135
D 9000 Gent Belgium

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Floppy mitral whistle heard across the room

To the Editor

The article by Dr Segall (Am Heart J 91 269 27? 1976) was of great interest to us at the University of Missouri Medical Center because we had a similar experience a week before the article was published

Dr Segall reported a 23 year-old young woman who heard a peculiar noise emanating from inside her chest at the age of twelve years, which soon disappeared but recurred occasionally during the next ten years. Echocardiography showed the classic midsystolic buckling of the mitral valve

Our patient A H (UMMC No 11 3 78-4) a seven year-old girl, was at home just before Christmas when she and her mother who was sitting across the room from her (estimate of 5 feet away) heard a peculiar squeaking rhythmic noise emanating from the girl s chest The mother trying to find the source of the squeak asked the girl to stop breathing and hold still for a moment To their surprise the squeak was still there and was synchronous with the girl s pulse

The mother immediately rushed her to the local physician and his nurse who confirmed the noise but could not make anything out of it other than a Grade VI/VI systolic murmur Since the child was healthy the physician reassured the family and arranged for the child to be seen in our Pediatric Cardiac Clinic

Our physical examination revealed a slender but healthy looking girl with no features to suggest Marfan s syndrome Our initial examination of the chest was completely normal except for a soft midsystolic click No murmur was heard with or without the stethoscope

Upon questioning the child and the mother further they told us that the squeak is not always heard it sometimes disappears for two to five days and when it is heard, it usually lasts for only a few minutes. They also stated that when the child runs home from school or when she is emotionally excited the whistle often recurs and the heart rate is usually around 120 per minute when the whistle is heard After asking the child to perform 10 sit ups to our surprise a Grade III/VI high pitched mid-systolic squeak was heard at the apex Cardiac catheterization with cineangiography was performed and the only abnormality found was a prolapse of the posterior leaflet of the mitral valve No mitral insufficiency was seen and the murmur and mid-systolic click disappeared during the two days of hospitalization

Our speculation about the origin of the sound is that the loose floppy mitral leaflets may enter a certain position at a certain body posture or activity resulting in a mild mitral insufficiency with fluttering of the loose mitral leaflets in the course of the jet stream of blood, thus creating the whistling sound

In 1880 William Osler reported an unusual heart murmur that could be heard at a distance of 3 feet and 2 inches from the chest wall of a 12 year-old well nourished girl That murmur also disappeared suddenly and could not be detected on most careful examination

To our knowledge this represents the third reported case of a floppy mitral whistle that can be heard across the room It is interesting that all these cases were females and that the whistle was heard for the first time at the ages seven to twelve years.

Zuhdi Lababidi M D
Director of Cardiology
Department of Child Health
University of Missouri School of Medicine
University of Missouri Medical Center
Columbia Mo 65201

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Letters to the Editor

Interpretation of findings using Holter ECG recordings

To the Editor

Holter recording has become a valuable part of the physician's armamentarium in the clinical diagnosis, evaluation and management of patients. But as noted with previous new or innovative diagnostic methods, its results can best be *correctly interpreted only when baseline observations of both* healthy and diseased populations using the new method have been established. As a result of the relative lack of such baseline Holter recording electrocardiographic observations, the danger of misinterpretation or overinterpretation of Holter recording studies of inhomogeneous populations without appropriate controls is greater. Such factors seem to be operative (at least in part) in the clinical report entitled "*Incidence of arrhythmias and ST segment changes in elderly* patients during barium enema studies" (AM HEART J 90: 688, 1975).

The authors examined a group of 58 hospitalized patients all over the age of 60 years with a standard 12 lead electrocardiogram, a resting 100 cycle rhythm strip (presumably 1 to 2 minutes) and then during a barium enema examination with Holter recording (indicated by the text as usually 10 to 45 minutes). Aspects of the study which warrant consideration prior to interpretation of the data include the control observations and the patients studied.

It has been previously recognized that Holter recordings (long or short duration) are a more sensitive method of detecting electrocardiographic abnormality in various populations than either a standard 12 lead electrocardiogram or a two minute electrocardiographic rhythm strip. Therefore it is not surprising that "new arrhythmias" (despite the relative stringent criteria chosen) were detected by Holter recording during the barium enema examination when compared to control 12 lead electrocardiograms or a control resting 100 cycle rhythm strip, for these arrhythmias may have been detected *with* or *without* the barium enema. A more appropriate *control for comparison might have included a Holter* recording of the same patient without the variables being examined (dehydration, fear, systemic arterial pressure changes, and barium enema examination) *with careful atten*tion to maintain the same clinical status, time of examination and medications. Even then, variability of cardiac dysrhythmia (day to day) would have to be considered. Thus to ascribe all of the arrhythmias of Fig. 1 to the incidence of new arrhythmias is both misleading and incorrect. *Prevalence* or the presence of cardiac dysrhythmia during barium enema examination was defined in this sample of hospitalized *patients*, not *incidence* or the risk of developing dysrhythmia during such an examination. These comments are especially pertinent when it is realized that the study population examined was *60 years old or older*. Although reference observation data of cardiac dysrhythmia in various populations (healthy and diseased) have not been totally defined, early studies indicate that *cardiac dysrhythmia increases with age* and as many as 81 per cent of one cohort of such men age 60 to 65 had ventricular arrhythmia detected by Holter recording. Thus a Holter recording examination of the selected patients even during usual activities would be expected to disclose appreciable cardiac dysrhythmia. Review of the authors' results in Table I indicates more "Positive *ECG during barium enema*" *in the older age* groups and suggests age per se was a factor in the findings. Whether such dysrhythmia in older persons is due to latent cardiac disease is unknown.

Notwithstanding these comments, it is understandable how the authors and others (myself included) might expect the barium enema examination with its associated stresses to have a provocative or causal influence on cardiac dysrhythmia. This risk of *new* cardiac dysrhythmia (i.e., incidence), however, may be surprisingly small, for as the authors stated, "the effect of evacuation of the barium and of distention of the *colon had little influence on our results*."

Thus, although I agree with the summary remarks in some respects, the study did not clearly define the incidence of developing arrhythmias and significant ST segment depression attributable to the barium enema examination and clinicians should be cautious not to derive an especially ominous inference with regard to the effects of the barium enema examination on cardiac dysrhythmia.

Harold L. Kennedy, M.D.
Department of Cardiovascular Services and Clinical Investigations
U.S. Public Health Service Hospital
3100 Wyman Park Drive
Baltimore, Md. 21211
Department of Social and Preventive Medicine
University of Maryland

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Left axis deviation

To the Editor

We were interested in the paper by Drs. Grayzel and Neyshaboori concerning the etiologic factors of left axis

The values of $C(t_a)$ t_a and s are then inserted into the appropriate equation to calculate Part 2 of each area Parts 1 and 2 are then added The formula for mean transit time as developed by Zierler[6] becomes

$$\bar{t} = \frac{\int_0^t C(t)\, t\, dt + \frac{C(t)}{s}\left(t + \frac{1}{s}\right)}{\int_0^t C(t)\, dt + \frac{C(t)}{s}}$$

This method was compared to planimetry to determine the area of several idealized curves with various exponential constants A total of about ten calculator entries were made for each calculation and the two methods differed on average by less than 5 per cent Therefore a high degree of accuracy is possible using a hand calculator without the tedious replotting of the curve on semilog paper

The advantage of numerical integration over planimetry or geometric approximations becomes apparent when mean transit time must be calculated An often used approximation of this mean is the time at half the curve area This represents the median transit time frequency and only corresponds to the mean when the curves are perfectly symmetrical Symmetry is rarely the case with indicator dilution curves as a greater dispersion of indicator occurs at the tail end of the curve True mean transit time is essential for the accurate calculation of the volume of distribution of an indicator as significant error may be introduced if the median transit time is used.

James C Parker Ph D
David H Pearce Ph D
Department of Physiology and Biophysics
University of Mississippi School of Medicine
2500 North State St
Jackson Miss 39216

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2 Yousof A M Endrys J and Bicik V Simple method of measuring dye curve area by planimetry using the half area method J Appl. Physiol 36 611 1974
3 Coleman T G and Criddle F J Jr Computerized analysis of indicator dilution curves J Appl. Physiol 28 358 1970
4 Hepner C F Jones G W Jacobs J II Kezdi P and Wessel H U Automatic computation of the area under indicator dilution curves IEEE Transactions on Communications and Electronics 83 358 1970
5 Jorfeldt L and Wahren J A simplified procedure for calculation of cardiac output from dye dilution curves Acta Med. Scand. Suppl. 470-476 p 75 1967
6 Zierler K L Circulation times the theory of indicator dilution methods for determining blood flow and volume in Handbook of Physiology Hamilton W F and Dow P eds. Washington D C 1962 Am Physiol Soc., Sec 2 Vol 1 pp 585-615

Indicator dilution flows and transit times with a pocket calculator

To the Editor

A number of methods have been devised for measuring the area under indicator dilution curves including geometric approximations planimetry or integration using digital or analog computers Graphical methods are often tedious and computer analysis necessitates access to expensive computing equipment The availability at modest cost of multifunction scientific calculators now makes numerical integration of the curve areas possible with a personal calculator A calculator we have found satisfactory for such computations is the Texas Instruments SR 51A which has statistical and linear regression capability

The well known equations for single injection dye dilution cardiac output and mean transit times are

$$Q = \frac{I}{\int_0^\infty C(t)\,dt}$$

$$\text{and } \bar{t} = \frac{\int_0^\infty C(t)\,t\,dt}{\int_0^\infty C(t)\,dt}$$

Where *I* is the amount of indicator injected *Q* is the flow *t* is the time and *C(t)* is the concentration of indicator measured as a function of time at some point down stream However practical application of these equations has been hampered by the tendency for early recirculation to obscure the latter portions of the curve Al o the integral in the numerator of the transit time formula cannot easily be obtained by graphical methods

These difficulties may be overcome by numerical integration of the concentration with respect to time The area under the indicator curve is treated as the two separate areas in Fig 1 Part 1 of the area may be integrated by several entries using the trapezoid rule C is assigned to the point of the initial rise in indicator concentration and C is assigned to a point where indicator concentration has fallen to about 80 per cent of the maximum rise The step size (Δt) is chosen to correspond to a convenient time division of the chart paper sufficient to divide the area into several parts Use of Δt = 1 whenever possible facilitates calculations when the following trapezoid integration scheme is employed

$$A = \int_0^t C(t)\,dt \quad = \Delta t(\,5\,C \;+ C \;+ C \;+ C \;+ C \;+ \,\cdot\,C\,)$$

For calculation of mean transit time

$$A = \int_0^t C(t)\,t\,dt \quad = \Delta t\,(\,\cdot\,C \;+ 1\,5\,C \;+ 2\,\cdot\,C \;+ 3\,5 \;+ [(n\;1) + \;5]\,C \;+ \;5n\,C\,)$$

The trapezoid rule for integration with large step sizes has the advantage of accuracy over rectangular approximations and ease of computation over parabolic segment integration Simpson s rule using parabolic segments affords a slight gain in accuracy but utilizes more complex coefficients If large rectangular steps are used for integration (Euler s method) a skew error is introduced when the curve does not return to the baseline Naturally any of these methods becomes more accurate as step size decreases

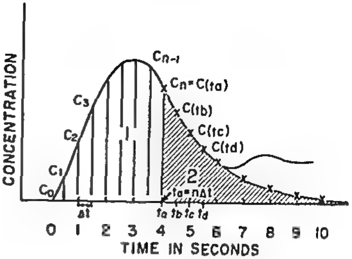

Fig 1 Diagram of a typical indicator dilution curve The vertically hatched area corresponds to Part 1 and the diagonally hatched area corresponds to Part 2 (see text)

Part 1 of the area may be integrated on the calculator by summing the concentration points in one memory and summing the product of the concentration point and appropriate coefficient in a second memory The totals for points C through C are then multiplied by Δt and Δt respectively as indicated in the above formulas These products are recorded and the calculator cleared

Part 2 of the total area is generally assumed to be the integral of a monoexponential extrapolated to the baseline at infinite time The area under this part of the curve is

$$A = \int_t^\infty C(t\,)\,e^{(\quad)}\,dt = \frac{C(t\,)}{s}$$

Part 2 of the frequency weighted area may be integrated by parts

$$A = \int_t^\infty C(t\,)\,t e^{(\quad)}\,dt = \frac{C(t\,)}{s}\,(t \;+ 1/s)$$

Thus only $C(t_a)$ t_a and *s* are required to calculate these areas $C(t_a)$ and t_a are known from the curve and *s* may be calculated either by using a least squares regression analysis of three or more points or direct calculation from two points on the exponential portion of the downslope On calculators set up for linear regression the exponential is linearized by entering the natural log of the indicator concentration Thus lnC(t) and t are entered as the first set of regression points and 2 to 4 other sets prior to obvious recirculation are al o selected The slope of the regression line is automatically computed by the best fit method of least squares This slope is the decay constant of the downslope exponential s The regression technique allows for a slight deviation of any one point from the true exponential In the event the calculator used has no regression capability *s* may be calculated from only two points C(t) is taken as the first point and C(t) from the exponential portion of the downslope is the second Since C(t) = C(t)e and C(t) = C(t)e

$$s = \frac{\ln \dfrac{C(t\,)}{C(t\,)}}{t \quad t}$$

The values of $C(t_o)$, t_m and s are then inserted into the appropriate equation to calculate Part 2 of each area. Parts 1 and 2 are then added. The formula for mean transit time as developed by Zierler[6] becomes

$$\bar{t} = \frac{\int_0^t C(t)\,t\,dt + \frac{C(t)}{s}\left(t + \frac{1}{s}\right)}{\int_0^t C(t)\,dt + \frac{C(t)}{s}}$$

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James C. Parker, Ph.D.
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Department of Physiology and Biophysics
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Book reviews

The Initiation of the Heartbeat By Denis Noble Oxford 1975 Clarendon Press 156 pages Price $13 95

Noble reviews the subject of the heartbeat from the electrophysiologic point of view The role of ions the nervous system and technics for studying the electrical and metabolic events associated with the heartbeat are discussed briefly and in a fashion that should interest beginners in cardiac physiology and electrophysiology The emphasis on ion fluxes in initiating the heart beat and electric activity is emphasized This book is lucid and brief and should interest medical students interns residents and fellows who are especially interested in electrocardiography

Advances in Cardiology vol [illegible] Integrated Medical-Surgical Care in Acute Coronary Artery Disease Edited by John H K Vogel Basel Switzerland 1975 S Karger AG 199 pages Price $1 , 2 ,

This publication summarizes the Fifth Cardiovascular Conference held at Snowmass at Aspen The entire conference was devoted to the experience and recommendations of the contributors to medical and surgical management of coronary heart disease The major part of the symposium was devoted to evaluation of coronary bypass surgery The results of the contributors are clearly described Although medical management was discussed the role of the cardiologists seemed to be concerned primarily with activities in the catheterization laboratory Cardiologists and cardiac surgeons will find this book to contain a great deal of valuable clinical data related to current results of medical and surgical care of patients with coronary heart disease

Electric Current Flow in Excitable Cells By J J B Jack D Noble and R W Tsien Oxford 1975 Clarendon Press 502 pages Price $45 00

This is an excellent summary of the pertinent electrophysiologic knowledge about the flow of current in cells The discussions are concerned mainly with nerve and muscle cells The presentations are highly technical for clinicians or clinical electrocardiographers but they should be extremely interesting and important to electrophysiologists and those in theoretic phases of nerve and muscle membrane potentials The cable theory as applied to nerve and muscle fibers is nicely discussed with the support of clear and simple illustrations The mathematical discussions are also good and useful but complex for clinicians The spread of the excitation and recovery potentials are discussed This is a very good highly technical book which is a fine addition to the library on electrophysiology The book is not to be merely read but should be studied

Recent Advances in Studies on Cardiac Structure and Metabolism volume [illegible] Basic Functions of Cations in Myocardial Activity Edited by A Fleckenstein and N S Dhalla Series editor G Rona Baltimore/London/Tokyo 1975 University Park Press 529 pages Price $39 50

This volume contains the many important papers presented at the Sixth Annual Meeting of the International Study Group for Research in Cardiac Metabolism held in Freiburg Germany in September 1973 The entire symposium was predominantly concerned with the role of ions in myocardial metabolism The biophysics of the sarcolemma subcellular calcium metabolism role of calcium in muscle contraction myocardial membrane dysfunction action of drugs on myocardial electrolyte metabolism and cardiac energetics were the main topics of discussion The many brief papers included in this book are extremely interesting and important Those who are engaged in a study of myocardial metabolism will find this symposium to be excellent The contributors were outstanding laboratories mainly of Europe and the USA

Circulatory Physiology II Dynamics and Control of the Body Fluids 1st edition By Arthur C Guyton M D Aubrey E Taylor Ph D and Harris J Granger Ph D Philadelphia/London/Toronto 1975 W B Saunders Company 397 pages Price $20 00

This is an important book which summarizes very well a great deal of important knowledge about body fluids tissue fluid dynamics and body fluid circulation The 23 chapters are well written and lucidly illustrated The presentations are thought provoking Guyton and associates discuss tissue pressure interstitial fluid space and fluid flow oncotic pressure of tissue fluids special fluid systems such as in the eye osmotic forces across the capillary walls and many other important physiologic problems related to tissue fluid dynamics The bibliography is good and the technics are clearly discussed This is a highly recommended book for all students interns residents and physiologists as well as for cardiologists

Books received

Medical Malpractice Law By Angela Roddey Holder J.D Somerset, N J 1975 John Wiley & Sons Inc. 561 pp Price $??.50

World Food Problems—A Selective Bibliography of Reviews By Miloslav Rechcigl, Jr B S Ph D Cleveland 1975 CRC Press, Inc 161 pp Price $33.35

The White Cell By Martin J Cline M D Cambridge Mass., 1975 Harvard University Press, 543 pp Price $35 00

Cardiologia D'Oggi By Alessandro Bereta Anguissola and Vittorio Puddu Turin 1975 C G Edizioni—Medico—Scientifiche 514 pp

The Saccharine Disease By T L Cleave M R C P New Canaan Conn 1975 Keats Publishing Company 192 pp Price $ 95

Cyclic Nucleotides in Disease Edited by Benjamin Weiss Baltimore Md 1975 University Park Press 388 pages. Price $14.50

Explorations in Aging Edited by Vincent J Cristofalo Jay Roberts and Richard C Adelman New York 1976 Plenum Publishing Corporation 293 pages Price $19 80

Developmental and Physiological Correlates of Cardiac Muscle Edited by Melvyn Lieberman and Toyomi Sano New York 1975 Raven Press 325 pages Price $25 00

Glucose Insulin Potassium and the Heart By Richard J Kones M D Mount Kisco N Y, 1975 Futura Publishing Company 440 pages. Price $48 00

1975 Year Book of Cardiovascular Medicine Edited by Harvey Kirkendall, Kirklin Nadas, Paul and Sonnenblick, Chicago 1975 Year Book Medical Publishers Inc., 441 pages.

Nurses Guide to Cardiac Monitoring By Peter Hubner M B Baltimore Md 1975 The Williams & Wilkins Company 61 pages. Price $6 00

Should Trees Have Standing? By Christopher D Stone Los Altos Calif., 1975 William Kaufmann Inc 94 pages

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Radioactive Microsphere Method symposium

The Radioactive Microsphere Method an official presym posium to the IXth World Conference on Microcirculation (Antwerp July 5 to 9 1976) will be held at Janssen Pharma ceutica Beerse Belgium on July 3 1976 For additional information please write Mary Laureyssens Secretary to the Symposium Janssen Research Foundation Koninklijke laan 17 2340 Beerse Belgium

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